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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Use of D4 and 5-HT2A antagonists, inverse agonists or partial agonists

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USE OF D4 AND 5-HT2A ANTAGONISTS, INVERSE AGONISTS OR PARTIAL AGONISTS

Field of the invention

The invention relates to the field of neuropsychiatry. More specifically, the invention relates to the use of compounds, which have D4 and 5-HT2A antagonist, inverse agonist or partial agonist activity, for the preparation of medicaments.

Background of the invention

Conventionally, mental disorders are divided into types based on criteria sets with defining features. DSM-IV *(American Psychiatric Association,* (1993 – ISBN 0 – 89042 – 061 – 0)) is the in the art well-known golden standard of such a categorical classification. In DSM-IV, there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder. There is also no assumption that all individuals described as having the same mental disorder are alike in all important ways. Individuals sharing a diagnosis are likely to be heterogeneous even in regard to the defining features of the diagnosis. Thus, the categorical defined mental disorders as mood and anxiety disorders are having an external and even internal variable co-incidence of symptoms concerning e.g. mood, anxiety, perception, feeding, somatic sensations, sexual functions, sleep, cognitive functioning, impulse control, attention, substance use, personality, bereavement, identity, phase of life, abuse or neglect and other aspects of behavior.

In a dimensional system, clinical presentations are classified based on quantification of attributes i.e. dysfunctions rather than the assignment to categories and works best in describing phenomena that are distributed continuously and that do not have clear boundaries.

Emotion dysregulation is known as such an attribution or dysfunction that plays an important role in the development and course of mental disorders *(Gross, J. J. & Munoz, R. F., 1995, Emotion regulation and mental health, Clinical Psychology: Science and Practice, 2, 151-164; Mennin, D.S., Heimberg, R. G., Turk, C. L. & Fresco, D. M., 2002, Applying an emotion regulation framework to integrative approaches to generalized anxiety disorder, Clinical Psychology: Science and Practice, 9, 85-90; Linehan, M. M., 1993, Cognitive-behavioral treatment of borderline personality disorder, New York, The Guilford Press; Gratz, K. L., Roemer, L., 2001 & 2004, Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation*

of the Difficulties in Emotion Regulation Scale, Annual meeting of the Association for Advancement of Behavior Therapy, Nov. 2001 & Journal of Psychopathology and Behavioral Assessment, Vol. 26, No. 1, March 2004) besides behavioural and cognitive dysfunctions. D4 dopamine receptors (D4DR), almost exclusively present in the mesocortical and mesolimbic systems *(O'Malley, K. L., Harmon, S., Tang, L., Todd, R. D., The rat dopamine D4 receptor: sequence, gene structure, and demonstration of expression in the cardiovascular system, New Biol., 4, 137-46, 1992)*, are in the art known as modulators of emotion and cognition. D4DR agonistic activity gives a behavioural sensitisation; D4DR antagonistic activity leads to an emotion modulation *(Svensson, T. H., Mathé, A. A., Monoaminergic Transmitter Systems, Biological Psychiatry (eds. D'Haenen, H., et al.), 45-66, 2002, John Wiley & Sons, Ltd).* Data demonstrate that agonism of the dopamine D4 receptors play an important role in the induction of behavioral sensitization to amphetamine and accompanying adaptations in pre- and postsynaptic neural systems associated with the mesolimbocortical dopamine projections *(D. L. Feldpausch et al.; The Journal of Pharmacology and Experimental Therapeutics Vol. 286, Issue 1, 497-508, July 1998).*

Results suggest that the antagonisms of cortical D2 dopamine receptors are a common target of traditional and atypical antipsychotics for therapeutic action. Higher *in vivo* binding to the D2 receptors in the cortex than in the basal ganglia is suggested as an indicator of favorable profile for a putative antipsychotic compound *(X. Xiberas and J.L. Martinot; The British Journal of Psychiatry (2001) 179: 503-508)*. Results show that dopamine D4 receptor antagonism in the brain does not result in the same neurochemical consequences (increased dopamine metabolism or hyperprolactinemia) observed with typical neuroleptics *(Smita Patel et al., The Journal of Pharmacology and Experimental Therapeutics Vol. 283, Issue 2, 636-647,1997).* The selective D4 dopamine receptor antagonist L-745,870 was ineffective as an antipsychotic for the treatment of neuroleptic responsive patients with acute schizophrenia *(Kramer, M.S. et al., Arch. Gen. Psychiatry 1997 Dec; 54(12):1080).*

Finally, in the biological system, mental disorders are defined on other levels of abstraction than in the categorical and dimensional system. Structural pathology (e.g. amyloid plaques in Alzheimer Disease), etiology (e.g. HIV Dementia) and deviance from a physiological norm (e.g. reduced cerebral blood flow) are often used as indicative biological markers for a mental disorder. The underlying dysregulation of various neurotransmittor systems (glutaminergic, GABAergic, cholinergic, monoaminergic (nor-

adrenergic, dopaminergic, serotonergic), etc.) is the in the art used model for the explanation of the biological determinants of the clinical presentation of mental disturbances. It is known that the Serotonin 2A Receptor (5-HT2A receptor) - which is widespread in the Central Nervous System (CNS) - has a regulating role on the dysregulation of various neuro-transmittor systems. 5-HT2A agonism gives several behavioural disturbances; 5-HT2A antagonism leads to a governance of mood, social behaviour, anxiety, cognitive function, stress, sleep functions, nociception, sexual functions, feeding and other aspects of behaviour *(J.E. Leysen (2004) 5-HT2 Receptors; Current Drug Targets – CNS & Neurological Disorders, 2004, 3, 11-26)*.

Dysregulation of the HPA axis (hypothalamic - pituitary - adrenal axis) has frequently been reported in patients with psychiatric disorders, and is among the most robustly demonstrated neurobiological changes among psychiatric patients *(D.A. Gutman and C.B. Nemeroff, Neuroendocrinology, Biological Psychiatry (eds. D'Haenen, H., et al), 99, 2002, John Wiley & Sons, Ltd)*. The resulting elevated plasma cortisol concentrations leads to an enhanced binding of serotonin for the 5-HT2A receptor *(E. A. Young, Mineralocorticoid Receptor Function in Major Depression, Arch Gen Psychiatry, Jan 2003; 60: 24 - 28)* and thus agonism.

Additionally 5-HT2A antagonism gives a des-inhibiting of the inhibitory effect of the 5-HT2A receptor on (i) the 5-HT1A receptor stimulation by serotonin *(S. M. Stahl, Newer Antidepressants and Mood Stabilizers, Essential Psychopharmacology, 265 , University Press; 2 edition (June 15, 2000); ISBN: 0521646154)* and on (ii) the dopamine release in the mesocortical systems *(S. M. Stahl, Classical Antidepressants, Serotonin Selective and Noradrenargic Reuptake Inhibitors, Essential Psychopharmacology, 233 , University Press; 2 edition (June 15, 2000); ISBN: 0521646154)*.

Clinical or real effectiveness of psychopharma is very rare via common pooping-out; many treatment-refractory patients and up to half of patients fail to attain remission *(S. M. Stahl, Essential Psychopharmacology, Depression and Bipolar Disorders, 151, University Press; 2 edition (June 15, 2000); ISBN: 0521646154)* . Implications of not attaining remission for Mental Disorders are increased relapse rates, continuing functional impairment and increased suicide rate *(S. M. Stahl, Essential Psychopharmacology, Depression and Bipolar Disorders, 152 , University Press; 2 edition (June 15, 2000); ISBN: 0521646154)*. Clinical causes of not attaining remission by the Current Psychopharmacological Compounds are inadequate early treatment, underlying emotion dysregulation (affecting instability – hypersensitivity – hyperaesthesia – dissociative phenomena, etc.) and

competitive antagonism. There is thus a growing need for a more efficient therapy and more efficient, selective and efficacious medicaments for treating mental disorders.

Summary of the invention

The present invention relates to the use of compounds and pharmaceutical compositions having D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity for the treatment of the underlying emotion dysregulation of mental disorders (e.g. affecting instability – hypersensitivity – hyperaesthesia – dissociative phenomena - etc.) and to methods entailing administering to a patient diagnosed as having a mental disorder a pharmaceutical composition containing (i) compounds having specific high selective D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity and (ii) a known medicinal compound and/or compositions of compounds. The combined D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic effects may reside within the same chemical or biological compound.

Taken into account the above mentioned (i) rare clinical or real effectiveness of psycho tropics, (ii) the governance of the features and dysfunctions responsible - in a variable co-incidentally – for the clinical state of the mental disorders by D4 dopamine receptor (D4DR) and 2A serotonin receptor (5-HT2A) antagonism and (iii) the fact that 5-HT2A antagonism gives a des-inhibiting of the inhibitory effect of the 5-HT2A receptor on (a) the 5-HT1A receptor stimulation by serotonin and on (b) the dopamine release in the mesocortical systems, the present invention relates to the use of a compound for the preparation of a medicament for treating a disease or disorder with an underlying emotion dysregulation, characterised in that said compound has (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors and wherein said compound is administered to a patient in a dose ranging between 5 and 15 mg of the active ingredient. Preferably, said compound is pipamperon.

In a preferred embodiment, in a mono therapeutic context, the invention relates to the use of a compound as defined above, preferably pipamperon, for preparing a medicament for treating a disease or disorder selected from the group comprising anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment

disorders, cognitive disorders, impulse control disorders, pervasive development, attention-deficit and disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational, identity, phase of life, academic problem, problems related to abuse or neglect.

According to a further embodiment the invention relates to the use of a first compound as defined above for the preparation of a medicament for treating a mental disease or disorder with an underlying emotion dysregulation whereby a second compound is administered simultaneously with, separate from or sequential to said first compound to augment the therapeutic effect of said second compound on said disease, or to provide a faster onset of the therapeutic effect of said second compound on said disease.

The mental diseases or disorders characterized by an underlying emotion dysregulation can be grouped into subclasses as follows: (i) non-cognitive mental disorders comprising mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect; (ii) cognitive diseases comprising delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders; (iii) pain disorders; and (iv) Parkinson Disease.

In a preferred embodiment, the first compound is administered daily at least one day before administering said second compound.

Preferably, said second compound is characterized by the physiological property of influencing positively the activity of the Central Nervous System.

The invention also relates to a method for preparing a compound having a selective D4 and 5-HT2A antagonist, reverse agonist or partial agonist activity comprising the following steps: (a) measuring the selective affinity of a test compound to the D4 receptor and

selecting a compound that has a pKi value equal to or greater than 8 towards the D4 receptor in respect to all the other D receptors, and measuring the selective efficacy of the selected compound to the D4 receptor and selecting a compound which is a selective antagonist, inverse agonist or partial agonist of the D4 receptor; (b) measuring the selective affinity of a test compound to the 5-HT2A receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the 5-HT2A receptor in respect to all the other 5HT receptors, and measuring the selective efficacy of the selected compound to the 5-HT2A receptor and selecting a compound which is a selective antagonist, inverse agonist or partial agonist of the 5-HT2A receptor; (c) identifying a compound which is selected in (a) and (b), (d) preparing the compound identified in (c).

The invention further also relates to a compound prepared by the described method.

Detailed description of the invention

The present inventors surprisingly found that compounds which have a high selective affinity towards the 5-HT2A receptor and which, at the same time have a high selective affinity towards the dopamine-4 (D4) receptor show an improved effect in treating underlying emotion dysregulation of mental disorders.

The compounds according to the invention may be chemical or biological in nature, or may be chemically synthesised. Preferably, the compounds of the invention are provided as a pharmaceutically acceptable salt.

One example of such a compound which has both a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors, and a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors is pipamperon. Pipamperon is the conventional name given for the compound of the formula 1'-[3-(p-Fluorobenzoyl)propyl]-[1,4'-bipiperidine]-4'-carboxamide. Pipamperon is also the active ingredient of for instance the commercially available Dipiperon (Janssen, Cilag B.V).

Further, the present inventors surprisingly found that the dosage of active ingredient for pipamperon in treatment (in monotherapy as well as in combination therapy as described in more detail further) could be very low compared to conventionally used dosages. Preferred dosages which, according to the invention, have been shown to be effective for treating these mental disorders, range between 5 and 15 mg per day or between 5 and 10

mg per day. More preferably, dosages of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 mg per day are used in treatment of the diseases of the invention. In conventional pipamperon treatment, the active ingredient is available in tablets of 40 mg per tablet or in solutions of 2 mg per drop. Conventional usage of high doses ranging from 40 to 360 mg is prescribed. For instance, for children up to the age of 14, doses corresponding with 2 to 6 mg per kg body weight are conventionally prescribed. The high selective affinity of pipamperon towards the 5-HT2A receptor and the D4 receptor is reflected in the low dosage which is needed for the treatment of the mental diseases listed below and also contributes to the efficacy of the treatment.

The mental disorders which can be treated using pipamperon in a mono therapy at such low doses are for instance anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, cognitive disorders, impulse control disorders, pervasive development, attention-deficit and disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational, identity, phase of life, academic problem, problems related to abuse or neglect.

Mental disorders such as depression are commonly treated with serotonin re-uptake inhibitors. Unfortunately, however, these compounds can give rise to side effects in use. Moreover, a substantial problem in most treatment of mental disorders is the non-response to selective serotonin re-uptake inhibitors (SSRIs). Also the onset of the therapeutic effect can be delayed undesirable.

A problem to be solved by the present invention is thus the provision of a more efficient therapy and efficient, highly selective and efficacious medicaments for treating mental disorders.

The inventors found that, for instance, the non-response to selective serotonin re-uptake inhibitors (SSRIs) in depression may be declared by (partial) inhibition of the 5-HT1A stimulation via 5-HT2A stimulation. Des-inhibition thereof via 5-HT2A antagonism seems to be an answer to this problem.

The present inventors found that a simultaneous or foregoing treatment with a compound having a high selective 5-HT2A antagonist, inverse agonist or partial agonist activity, could lead to a greater response towards, for instance, SSRIs. However, not all compounds exhibiting 5-HT2A antagonism are useful: competition between 5-HT2A stimulation via

serotonin and 5-HT2A antagonism via the compound could be responsible for the lack of more efficacy of compounds which have both a selective serotonin re-uptake inhibitory and 5-HT2A antagonist profile, such as trazodone and nefazodone.

The present inventors further surprisingly found that a simultaneous or foregoing treatment with a compound having a high selective D4 antagonist, inverse agonist or partial agonist activity in combination with a compound having a high selective 5-HT2A antagonist, inverse agonist or partial agonist activity could lead to a greater response towards, for instance, SSRIs.

In this invention, the term "antagonist" refers to an interaction between chemicals in which one partially or completely inhibits the effect of the other, in particular agents having high affinity for a given receptor, but which do not activate this receptor.

In this invention, the term "inverse agonist" refers to a ligand which produces an effect opposite to that of the agonist by occupying the same receptor.

In this invention, the term "agonist" relates to an agent which both binds to a receptor and has an intrinsic effect.

In this invention, the term "partial agonist" relates to an agent with lower intrinsic activity than a full agonist, and which produces a lower maximum effect.

The present inventors found that a compound which binds to the 5-HT2A receptor with a pKi of at least 8 but for which the binding affinity, i.e. pKi, towards other 5HT receptors is less than 8 in combination with a high selective affinity for the D4 receptor, i.e. which bind to the D4 receptor with a pKi of at least 8 but for which the binding affinity, i.e. pKi, towards other dopamine receptors is less than 8 also show such an improved effect in treatment. These effects, i.e. D4 antagonism, inverse agonism or partial agonism and 5-HT2A antagonism, inverse agonism or partial agonism, may reside in the same compound.

The term "other 5HT receptors" as used herein relate to for instance 5-HT1 receptors (e.g. 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F), 5-HT2B, 5-HT2C, 5-HT6 (rat) and 5-HT7 (rat).

By the expression "selective affinity for the 5-HT2A receptor" is meant that the receptor has a higher affinity for the 5-HT2A receptor than for other 5-HT receptors.

The expression "selective affinity for the D4 receptor" means that the receptor has a higher affinity for the dopamine D4 receptor than for other dopamine receptors.

The term "other dopamine receptors" are, for instance, D1, D2 and D3 dopamine receptors.

pKi values of test compounds for dopamine receptors as well as 5-HT2A receptors can be measured using commonly known assays.

Compounds which have a selective affinity for the D4 receptor preferably have a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors.

Preferably, the compounds of the invention which have a selective affinity for the 5-HT2A receptor (or the D4 receptor), are compounds which have a pKi value equal to or higher than 8 towards the 5-HT2A receptor and the D4 receptor, and less than 8 towards other 5-HT receptors or dopamine receptors, respectively, as can be measured, for instance by methods known in the art. For instance, the "NIMH Psychoactive Drug Screening Program (PDSP)" K_i database (http://kidb.cwru.edu/nimh/5htp.php), is a unique resource in the public domain which provides information on the abilities of drugs to interact with an expanding number of molecular targets. The PDSP K_i database serves as a data warehouse for published and internally-derived pKi, or affinity, values for a large number of drugs and drug candidates at an expanding number of G-protein coupled receptors, ion channels, transporters and enzymes. The PDSP internet site also provides for commonly used protocols and assays for measuring pKi values of 5-HT and dopamine receptors.

A preferred example of a compound which has both a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors, and a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors and which is therefore useful in a combination therapy is pipamperon.

Table 1 illustrates the selective affinity of for instance pipamperon for the 5-HT2A and for the D4 receptor. In addition, Table 1 also illustrates the low or absence of affinity of pipamperon for other receptors such as the adrenergic receptors Alpha 1A, Alpha 2A, Alpha 2B, Alpha 2C, Beta 1, Beta 2, and the histamine receptor H1. As such, treating patients with pipamperon will provide for less side effects which otherwise result from simultaneous stimulation of other receptors. Therefore, and according to preferred embodiments, useful compounds according to the invention not only have a selective 5-HT2A and/or D4 affinity but also a low affinity for other receptors such as the adrenergic and histamine receptors.

The low dosage which can be used in pipamperon treatment, as already described earlier, contributes to the high selective affinity of the compound towards the 5-HT2A receptor and the D4 receptor and therefore also to the efficacy of the treatment.

The mental diseases or disorders characterized by an underlying emotion dysregulation can be grouped into subclasses as follows: (i) the non-cognitive mental disorders comprising mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect; (ii) cognitive diseases comprising delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfedt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders; (iii) the pain disorders; and (iv) Parkinson Disease. In Table 5, this classification has been used for summarizing the diseases and disorders relative to known psychotropics. In Table 6, an overview of pharmacological grouping is provided, indicating the pharmalogical profile numbering, the pharmalogical profile, the main disease or disorder indication(s), the name of the compound, the dose range, and the company producing or selling said compound.

These diseases and their diagnosis are very clearly defined in the "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)" published by the American Psychiatric Association. This manual sets forth diagnostic criteria, descriptions and other information to guide the classification and diagnosis of mental disorders and is commonly used in the field of neuropsychiatry. It is for instance available on the internet under: http://www.behavenet.com/ capsules/disorders/ dsm4tr.htm.

The expression "non-cognitive diseases or disorders" used in some of the embodiments of the invention comprises the following group of diseases or disorders: mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders,

impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect.

In other embodiments of the invention, the mental diseases or disorders that are characterized by an underlying emotion dysregulation belong to the group of pain disorders. For instance, the combination therapy with pipamperon is especially advantageous for management of acute pain in diseases such as, but not limited to, musculoskeletal diseases, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. For the classification of pain disorders, reference is also made to the DSM-IV where these disorders are clearly described in the section of somatoform disorders by way of internationally accepted diagnostic criteria.

In other embodiments of the invention, the 5-HT2A receptor and/or Dopamine-4 receptor antagonist, inverse agonist or partial agonist (e.g. pipamperon) is used in treatment of patients having neuro-degenerative diseases or disorders, or related cognitive diseases or disorders. The diseases or disorders of the present invention are characterized by an underlying degeneration of the Central Nervous System (CNS), preferably selected from the group consisting of, but not limited to, neurodegenerative diseases such as Parkinson Disease, and in other embodiments of the invention, selected from the group of (related) cognitive diseases or disorders such as Alzheimer Disease.

For instance, Parkinson Disease, which is a chronic progressive nervous disease chiefly of later life, is linked to decreased dopamine production in the substantia nigra and is marked by tremor and weakness of resting muscles and by a shuffling gait. Dopamine agonists and even levodopa, widely used in Parkinson Disease, gives via a dopamine D4 receptor stimulation psychiatric manifestations. The induced release of serotonin acts via 5-HT2A stimulation as a "brake" on dopamine release *(Young B.K., Camicioli R., Ganzini L., Neuropsychiatric adverse effects of antiparkinsonian drugs. Characteristics, evaluation and treatment. Drugs Aging. 1997 May;10(5):367-83).* Because of the need of specific D4 and 5-HT2A antagonism in the treatment of Parkinson Disease with dopamine agonists and even levodopa, it seems reasonable to combine with a compound with a high selective D4 and 5-HT2A antagonism i.e. having merely no activity towards the other receptors especially the D2 receptor because of the primary need of the relieve of the excessive burden of remaining dopaminergic neurons. Therefore, the use of the so-called atypical anti-psychotics or serotonin-dopamine antagonists (SDAs) is absolutely contra-

indicated since their high affinity for the D2 receptor. Even the use of serotonin releasing compounds such as SSRIs in the absence of an effective 5-HT2A antagonism are contra-productive towards the Parkinson Disease symptoms although many Parkinson patients are in need for an antidepressant since major depression is a very common and disabling condition in this kind of patients.

The expression "(related) cognitive diseases or disorders" according to the invention comprises, the following group of diseases or disorders: delirium (F05), dementia (such as Alzheimer Disease (F00), vascular dementia (F01), dementia due to other general medical conditions (HIV disease (F02.4), head trauma (F06.8), Parkinson Disease (F02.3), Huntington Disease (F02.2), Pick Disease (F02.0), Creutzfeldt-Jacob Disease (F02.1) and. other (F02.8)), substance-induced persisting dementia (F1x.6)), amnestic disorders due to a general medical condition (F06.8) or a substance-induced persisting amnestic disorder (F1x.6), mild cognitive impairment disorder (F06.7) and other cognitive disorders (F04). The above list of diseases is provided by way of example and is not intended to limit the invention.

For instance, Alzheimer Disease is a degenerative brain disease of unknown cause that is the most common form of dementia. Alzheimer Disease usually starts in late middle age or in old age as a memory loss for recent events spreading to memories for more distant events and progresses over the course of five to ten years to a profound intellectual decline characterized by dementia and personal helplessness. The disease is marked histologically by the degeneration of brain neurons especially in the cerebral cortex and by the presence of neurofibrillary tangles and plaques containing beta-amyloid. Because dopamine receptor D4 (DRD4) antagonism can inhibit the behavioral disturbances – merely aggression and confusion - caused by the degeneration of dopamine D2 receptors *(Esiri, M.M., The basis for behavioural disturbances in dementia, J. Neurol. Neurosurg. Psychiatry, 1996; 61(2):127–130.2)* accompanied with Alzheimer disease and 5-HT2A antagonism has an important boosting effect towards the effect of cholinesterase inhibitors such as used in the treatment by facilitating the affected dopamine release in the mesocortical dopamine pathways, a high selective D4/5-HT2A-antagonist would be a more preferable compound to combine with a cholinesterase inhibitor since this avoids the counteracting effect of the in the art used SDAs on the cognitive functioning by its dopamine receptor D2-antagonism.

These diseases and their diagnoses are very clearly defined in the "*International Statistical Classification of Diseases and Related Health Problems, 1989 Revision, Geneva, World Health Organization, 1992 (ICD-10)*. This manual sets forth diagnostic

criteria, descriptions and other information to guide the classification and diagnosis of neurodegenerative disorders and is commonly used in the field of neurology. According to the ICD-10 classification, the cognitive disorders are classified under several classes of disorders, i.e. dispersed under categories F00 to F19 (see above: respective classification between parentheses). Following the DSM classification, however, they are grouped in one class of diseases or disorders.

The terms "treatment", "treating", and the like, as used herein include amelioration or elimination of a developed mental disease or condition once it has been established or alleviation of the characteristic symptoms of such disease or condition. As used herein these terms also encompass, depending on the condition of the patient, preventing the onset of a disease or condition or of symptoms associated with a disease or condition, including reducing the severity of a disease or condition or symptoms associated therewith prior to affliction with said disease or condition. Such prevention or reduction prior to affliction refers to administration of the compound or composition of the invention to a patient that is not at the time of administration afflicted with the disease or condition. "Preventing" also encompasses preventing the recurrence or relapse-prevention of a disease or condition or of symptoms associated therewith, for instance after a period of improvement. It should be clear that mental conditions may be responsible for physical complaints. In this respect, the term "treating" also includes prevention of a physical disease or condition or amelioration or elimination of the developed physical disease or condition once it has been established or alleviation of the characteristic symptoms of such conditions.

As used herein, the term "medicament" also encompasses the terms "drug", "therapeutic", "potion" or other terms which are used in the field of medicine to indicate a preparation with therapeutic or prophylactic effect.

The present inventors not only found that the selective 5-HT2A and D4 antagonists, inverse agonists or partial agonists have an effect in augmenting the therapeutic effect or in providing a faster onset of the therapeutic effect of a diversity of other pharmaceutical compounds, i.e. also named "second compounds" in the present invention, in the treatment of specific diseases or disorders. A few examples of other pharmaceutical compounds whose effects are augmented or where the onset of the effect is fastened upon simultaneous or fore-going treatment with a selective 5-HT2A and D4 antagonist, preferably pipamperon in a low dose, are nor-epinephrine re-uptake inhibitors, neuroleptic agents, dopamine antagonists, or compounds used for treating or alleviating musculoskeletal diseases or disorders. A further list of other pharmaceutical compounds

or second compounds useful according to the invention is provided in Table 5. It should be clear, given the general applicable character of the invention, that this list of other pharmaceutical compounds is very brief and that the invention should not be restricted to the ones exemplified herein. It should be clear that in the present invention, pipamperon is never to be seen as a "second compound".

According to the invention, it thus has been found that the compounds having a selective 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity as described above are useful for augmenting the therapeutic effect of a second compound on a disease.

According to another embodiment of the invention, it has also been found that the compounds having a selective 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity as described above are useful for providing a faster onset of the therapeutic effect of a second compound on a disease.

From the above it should be clear that the selective 5-HT2A and D4 antagonist, inverse agonist or partial agonist is also named 'the first compound' in the embodiments of the invention.

According to the invention, when the 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity reside in separate compounds, the term "composition" may be used. Compositions of the invention comprise a first element having (i) a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors, and a second element having (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors.

The expression "the 5-HT2A and D4 antagonist, inverse agonist or partial agonist" is used herein to indicate a single compound having both activities or to indicate the composition comprising the activities in separate elements.

It should be clear that when, in the present invention, a composition of separate elements is used instead of a single compound, this composition of separate elements may be used in combination with another, i.e. a second, compound to augment the therapeutic effect of the other, i.e. the second, compound on the same or another disease.

When the 5-HT2A and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements and the second compound are administered simultaneously, the compounds or active ingredients may be present in a single pharmaceutical composition or formulation. Alternatively the compounds or active ingredients are administered in separate pharmaceutical compositions or formulations for simultaneous or

separate use. The invention thus also relates to pharmaceutical compositions comprising pipamperon and a second compound of the invention and to the uses of these pharmaceutical compositions.

When the 5-HT2A and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements of the invention are administered prior to the second compound as defined, the 5-HT2A and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements is administered at least during 1 day prior to said second compound. Preferably, the 5-HT2A and D4 antagonist, inverse agonist or partial agonist (e.g. pipamperon) or the composition comprising both elements is administered for at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 days prior to the administration of the second compound. Preferably, the 5-HT2A and D4 antagonist, inverse agonist or partial agonist (e.g. pipamperon) or the composition comprising both elements is administered for at least 2, 3, 4 or 5 weeks prior to the administration of the second compound, or even for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months prior to the administration of the second compound.

According to a preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of citalopram or for providing a faster onset of the therapeutic effect of citalopram.

Citalopram or citalopram hydrobromide is a selective serotonin (5-hydroxytryptamine / 5-HT) re-uptake inhibitor (SSRI) and is the conventional name given for the compound of the formula (RS)-1-[3-(dimethylamino)propyl]-1-(p-flurophenyl)-5-phthalancarbonitrile hydro-bromide.

According to an embodiment, a daily dose of active ingredient of SSRI, preferably citalopram, ranges between 10 and 40 mg per day. Preferably, daily doses of active ingredient ranging between 20 and 30 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.

According to another preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of citalopram or for providing a faster onset of the therapeutic effect of fluvoxamine.

Fluvoxamine or fluvoxamine maleate (luvox, fevarin) is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime

ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl) oxime maleate (1:1).

According to an embodiment, a daily dose of active ingredient of fluvoxamine maleate ranges between 100 and 300 mg per day. Preferably, daily doses of active ingredient ranging between 150 and 200 mg per day are administered. More preferably, a daily dose of 100, 150, 200, 250 or 300 mg per day is administered.

Most of the second compounds herein described are known in the art and may be used in doses according to the supplier's or physician's prescription, or may be used according to specific embodiments described herein.

Also encompassed by the invention are pro-drugs to these second compounds or active metabolites of these compounds. For instance, for risperidone it is known that, among other products, bio transformation in the liver produces 9-hydroxyrisperidone, which is of the same pharmacological activity and intensity as parent risperidone. Therefore, also 9-hydroxyrisperidone, naturally produced or chemically synthesized may be used in the methods and uses according to the invention.

The term "active metabolite" as used herein relates to a therapeutically active compound produced by the metabolism of a parent drug. Drugs administered to treat diseases are usually transformed (metabolized) within the body into a variety of related chemical forms (metabolites), some of which may have therapeutic activity (an active metabolite).

The present invention also encompasses the use of these second compounds, administered in the form of a pharmaceutically acceptable salt in admixture with a suitable pharmaceutically acceptable excipient.

To prepare the pharmaceutical compositions, comprising the compounds or the combination of the first and second compound described herein, an effective amount of the active ingredients, in acid or base addition salt form or base form, is combined in admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, for administration orally, nasal, rectally, percutaneously or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders,

disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included.

The pharmaceutical compounds for treatment are intended for parenteral, topical, oral or local administration and generally comprise a pharmaceutically acceptable carrier and an amount of the active ingredient sufficient to reverse or prevent the bad effects of mental disorders. The carrier may be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the compound, and by the route of administration.

Examples of pharmaceutically acceptable acid addition salts for use in the present inventive pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, p-toluenesulphonic acids, and arylsulphonic, for example.

The pharmaceutically acceptable excipients described herein, for example, vehicles, adjuvants, carriers or diluents, are well-known to those who are skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one that is chemically inert to the active compounds and one that has no detrimental side effects or toxicity under the conditions of use.

The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administration are merely exemplary and are in no way limiting. Overall, the requirements for effective pharmaceutical carriers for parenteral compositions are well known to those of ordinary skill in the art. See Pharmaceutics and Pharmacy Practice, J.B. Lippincott Company, Philadelphia, PA, Banker and Chalmers, eds., pages 238-250, (1982), and ASHP Handbook on Injectable Drugs, Toissel, 4th ed., pages 622-630 (1986). Topical formulations, including those that are useful for transdermal drug release, are well-known to those of skill in the art and are suitable in the context of the present invention for application to skin.

Formulations suitable for oral administration require extra considerations considering the nature of the compounds and the possible breakdown thereof if such compounds are administered orally without protecting them from the digestive secretions of the

gastrointestinal tract. Such a formulation can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients as are known in the art.

The compounds of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. For aerosol administration, the compounds are preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of compounds are 0.01%-20% by weight, preferably 1%-10%. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute 0.1%-20% by weight of the compounds, preferably 0.25-5%. The balance of the compounds is ordinarily propellant. A carrier can also be included as desired, e.g., lecithin for intranasal delivery. These aerosol formulations can be placed into acceptable pressurized propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer. Such spray formulations may be used to spray mucosa.

It will be understood that, apart from daily doses, the compounds can be administered by other schedules. For instance, the present invention also contemplates depot injection, in which a long acting form of the active compound is injected into the body, such as the muscles. From there the active compound slowly enters the rest of the body, so one injection can last from 1 to 4 weeks or even multiple months. Other form of dosage administrations relate to "once-a-week" pills, in which the ingredient is slowly released over a period of a week, and slow-realese patches, e.g. a CDS (Continuous Delivery System), or Once-a-Day Transdermal Patches.

According to a further embodiment, the invention also relates to a method for preparing a compound or composition having a selective D4 and 5-HT2A antagonist, reverse agonist or partial agonist. The invention also relates to the compounds prepared by the claimed method, with the proviso that said compound is not an already known compound, such as pipamperon.

It should be clear that the compounds and compositions described herein are useful for treating any patient in need thereof. As used herein the term "patient" is not restricted to humans but also to other mammals, for instance, domestic animals which may also suffer from any form of a mental disease or disorder described herein.

The second compounds of the invention can be further grouped according to their pharmacological profile, which is summarized in Table 6.

The present invention is now described in more detail by the following embodiments. The compounds belonging to different pharmacological profiles can be further grouped according to their action on the same pathway or system as follows.

1: combination therapy with a 5-HT (serotonin) reuptake enhancer

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT (serotonin) reuptake enhancer, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT (serotonin) reuptake enhancer compound is tianeptine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, tianeptine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT (serotonin) reuptake enhancer, preferably tianeptine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorder, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

A pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT (serotonin) reuptake enhancer is tianeptine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

2: combination therapy with a 5-HT1 autoreceptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1 autoreceptor agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1 autoreceptor agonist compound to augment

the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1 autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1 autoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1 autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT1 autoreceptor agonist compound is sunepitron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1 autoreceptor agonist, preferably sunepitron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorder, antisocial behaviour, bereavement occupational problem, problems related to abuse or neglect and pain disorders.

3: combination therapy with a 5-HT1A (serotonin 1A receptor) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1A (serotonin 1A receptor) agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders,

premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention further also relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention further also relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention further also relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT1A (serotonin 1A receptor) agonist compound is chosen from the group consisting of MN-305, zalospirone, xaliproden, VPI-013 (also known as OPC-14523), tandosprione, sarizotan, PRX-00023, metanospirone, lesopitron, gepirone, flesinoxan, EMD 68843, buspirone, bupropion (preferably controlled release formulation) and alnespirone, preferably xaliproden, sarizotan, gepirone, flesinoxan and bupropion (preferably controlled release formulation) or a pro-drug or an active metabolite thereof,

or a pharmaceutically acceptable salt thereof. More preferably, said 5-HT1A (serotonin 1A receptor) agonist is xaliproden and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient. Even more preferably, said 5-HT1A (serotonin 1A receptor) agonist is buproprion (controlled release formulation) and is to be administered in a daily dose ranging between 150 and 450 mg of the active ingredient. Even more preferably, said 5-HT1A (serotonin 1A receptor) agonist is gepirone and is to be administered in a daily dose, ranging between 20 and 80 mg of the active ingredient per day.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1A (serotonin 1A receptor) agonist, preferably chosen from the group consisting of MN-305, zalospirone, xaliproden, VPI-013 (also known as OPC-14523), tandosprione, sarizotan, PRX-00023, metanospirone, lesopitron, gepirone, flesinoxan, EMD 68843, buspirone, bupropion (preferably controlled release formulation) and alnespirone, more preferably xaliproden, sarizotan, gepirone, flesinoxan and bupropion (preferably controlled release formulation), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT1A (serotonin 1A receptor) agonist is xaliproden, preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT1A (serotonin 1A receptor) agonist is buproprion (controlled release formulation), preferably provided in a unitary dose of between 150 and 450 mg of the active ingredient.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT1A (serotonin 1A receptor) agonist is gepirone, preferably provided in a unitary dose of between 20 and 80 mg of the active ingredient.

4: combination therapy with a 5-HT1A (serotonin 1A receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1A (serotonin 1A receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT1A antagonist compound is chosen from the group consisting of robalzotan tartrate hydrate and NAD299 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1A antagonist, preferably chosen from the group consisting of robalzotan tartrate hydrate and NAD299, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

5: combination therapy with a 5-HT1B (serotonin 1B receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1B (serotonin 1B receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders,

adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT1B antagonist compound is chosen from the group consisting of elzasonan, AZD1134 and AR-A2, preferably elzasonan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1B antagonist, preferably chosen from the group consisting of elzasonan, AZD1134 and AR-A2, preferably elzasonan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

<u>6: combination therapy with a 5-HT2B (serotonin 2B receptor) antagonist compound</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT2B (serotonin 2B receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality

disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT2B antagonist compound is agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, agomelatine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT2B antagonist, preferably agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for

simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

A pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT2B antagonist is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

7: combination therapy with a 5-HT2C (serotonin 2C receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT2C (serotonin 2C receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2C antagonist compound to augment the therapeutic effect or to

provide a faster onset of the therapeutic effect of said 5-HT2C antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2C antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2C antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT2C antagonist compound is chosen from the group consisting of SB 243213 and agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, agomelatine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT2C antagonist, preferably chosen from the group consisting of SB 243213 and agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT2C antagonist is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

8: combination therapy with a 5-HT3 (serotonin 3 receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT3 (serotonin 3 receptor) antagonist compound, are substance-related disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance-related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT3 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT3 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT3 antagonist compound is ondansetron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, ondansetron is to be administered in a daily dose ranging between 8 and 32 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT3 antagonist, preferably ondansetron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of substance-related disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient, and wherein said 5-HT3 antagonist is ondansetron, preferably provided in a unitary dose of between 8 and 32 mg of the active ingredient.

9: combination therapy with a 5-HT6 (serotonin 6 receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT6 (serotonin 6 receptor) antagonist compound, are chosen from the group of

diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT6 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT6 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT6 antagonist compound is chosen from the group consisting of SB-271046, 742457 and 271046 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT6 antagonist, preferably chosen from the group consisting of SB-271046, 742457 and 271046 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-

Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

10: combination therapy with an acetylcholinesterase inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an acetylcholinesterase inhibitor compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an acetylcholinesterase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said acetylcholinesterase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said acetylcholinesterase inhibitor compound is chosen from the group consisting of tacrine, rivastigmine tartrate, rivastigmine, physostigmine, phenserine tartrate, metrifonate, huperzine A, galantamine (preferably extended release formulation), donezepil, dichlorvos and anseculin hydrochloride, preferably tartrate, or a pro-drug or an

active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, rivastigmine tartrate is to be administered in a daily dose ranging between 3 and 12 mg of the active ingredient. Preferably, phenserine tartrate is to be administered in a daily dose ranging between 20 and 30 mg of the active ingredient. Preferably, galantamine (extended release formulation) is to be administered in a daily dose ranging between 8 and 24 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an acetylcholinesterase inhibitor, preferably chosen from the group consisting of tacrine, rivastigmine tartrate, rivastigmine, physostigmine, phenserine tartrate, metrifonate, huperzine A, galantamine (preferably extended release formulation), donezepil, dichlorvos and anseculin hydrochloride, preferably tartrate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is rivastigmine tartrate, preferably provided in a unitary dose of between 3 and 12 mg of the active ingredient.

The invention further relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is phenserine tartrate, preferably provided in a unitary dose of between 20 and 30 mg of the active ingredient.

In addition, the invention relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is galantamine (preferably

extended release formulation), preferably provided in a unitary dose of between 8 and 24 mg of the active ingredient.

11: combination therapy with an adenosine A2a receptor antagonist compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an adenosine A2a receptor antagonist compound, is Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adenosine A2a receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adenosine A2a receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said adenosine A2a receptor antagonist compound is KW-6002 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, KW-6002 is to be administered in a daily dose ranging between 40 and 80 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an adenosine A2a receptor antagonist, preferably KW-6002 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is KW-6002, preferably provided in a unitary dose of between 40 and 80 mg of the active ingredient.

12: combination therapy with an adrenergic transmitter releaser

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an adrenergic transmitter releaser, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said adrenergic transmitter releaser compound is pipoxazole or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, pipoxazole is to be administered in a daily dose ranging between 30 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an adrenergic transmitter releaser, preferably pipoxazole, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said adrenergic transmitter releaser is pipoxazole, preferably provided in a unitary dose of between 30 and 60 mg of the active ingredient.

13: combination therapy with an alpha 1 adrenoreceptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an alpha 1 adrenoreceptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating

disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said alpha 1 adrenoreceptor antagonist compound is chosen from the group consisting of SDZ NVI 085 and flesinoxan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an alpha 1 adrenoreceptor antagonist, preferably chosen from the group consisting of SDZ NVI 085 and flesinoxan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and Parkinson disease.

14: combination therapy with an alpha 2 adrenoreceptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an alpha 2 adrenoreceptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is

to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said alpha 2 adrenoreceptor antagonist compound is chosen from the group consisting of UK-14304, sunepitron, mirtazepine, idazoxan, fluparoxan, A75200 and (R)-A 75200, preferably sunepitron or idazoxan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, idazoxan is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an alpha 2 adrenoreceptor antagonist, preferably chosen from the group consisting of UK-14304, sunepitron, mirtazepine, idazoxan, fluparoxan, A75200 and (R)-A 75200, preferably sunepitron or idazoxan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient

and wherein said alpha 2 adrenoreceptor antagonist is Idazoxan, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.

15: combination therapy with an AMPA receptor mediator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor mediator compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further

characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said AMPA receptor mediator compound is chosen from the group consisting of ampakine ORG 24448/CX-619, ampakine CX-717, ampakine CX-691 and ampakine CX-516, preferably ampakine ORG 24448/CX-619, ampakine CX-717 or ampakine CX-691, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an AMPA receptor mediator, preferably chosen from the group consisting of ampakine ORG 24448/CX-619, ampakine CX-717, ampakine CX-691 and ampakine CX-516, preferably ampakine ORG 24448/CX-619, ampakine CX-717 or ampakine CX-691, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

16: combination therapy with an amphetamine compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an amphetamine compound, are attention-deficit disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention deficit disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an amphetamine compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said amphetamine compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said amphetamine compound is methylphenidate (preferably administered by the transdermal system) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an amphetamine, preferably methylphenidate (preferably administered by the transdermal system) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of attention deficit disorders.

17: combination therapy with an amyloid aggregation-inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an amyloid aggregation-inhibitor compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an amyloid aggregation-inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said amyloid aggregation-inhibitor compound, further

characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said amyloid aggregation-inhibitor compound is chosen from the group consisting of APAN and Alzhemed, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, Alzhemed is to be administered in a daily dose of between 200 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an amyloid aggregation-inhibitor, preferably chosen from the group consisting of APAN and Alzhemed, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said amyloid aggregation-inhibitor is Alzhemed, preferably provided in a unitary dose of between 200 and 300 mg of the active ingredient.

18: combination therapy with an androgen receptor modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an androgen receptor modulator compound, are sexual and gender identity disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered

simultaneously with, separate from or prior to the administration of an androgen receptor modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said androgen receptor modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said androgen receptor modulator compound is LGD2226 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an androgen receptor modulator, preferably LGD2226 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of sexual and gender identity disorders.

19: combination therapy with an beta 3 adrenoreceptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an beta 3 adrenoreceptor agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of

a beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said beta 3 adrenoreceptor agonist compound is SR 58611 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a beta 3 adrenoreceptor agonist, preferably SR 58611 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

<u>20: combination therapy with a calcium channel modulator compound</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a calcium channel modulator compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia,

vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said calcium channel modulator compound is chosen from the group consisting of safinamide and MEM 1003, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a calcium channel modulator, preferably chosen from the group consisting of safinamide and MEM 1003, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson disease.

21: combination therapy with a cannabioid receptor 1 (CB1) antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a cannabioid receptor 1 (CB1) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said

pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabioid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabioid receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabioid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabioid receptor 1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabioid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabioid receptor 1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment the invention relates to the uses as described above, wherein said cannabioid receptor antagonist compound is SR 141716 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a cannabioid receptor antagonist, preferably SR 141716 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of

diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

22: combination therapy with a cathepsin K inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a cathepsin K inhibitor compound, are pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cathepsin K inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cathepsin K inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said cathepsin K inhibitor compound is 462795 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a cathepsin K inhibitor, preferably 462795 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain disorders.

23: combination therapy with a choline uptake enhancer compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a choline uptake enhancer compound, are chosen from the group of diseases or

disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a choline uptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said choline uptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said choline uptake enhancer compound is MKC-231 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, MKC-231 is to be administered in a daily dose of between 20 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a choline uptake enhancer, preferably MKC-231 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,

dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said choline uptake enhancer is MKC-231, preferably provided in a unitary dose of between 20 and 160 mg of the active ingredient.

24: combination therapy with a COX-2 inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a COX-2 inhibitor compound, are pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a COX-2 inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said COX-2 inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said COX-2 inhibitor compound is chosen from the group consisting of valdecoxib, rofecoxib, parecoxib, etoricoxib, COX 189, celecoxib and ABT-963, preferably parecoxib, etoricoxib or COX 189, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, parecoxib is to be administered in a daily dose of between 20 and 80 mg of the active ingredient. Preferably, etoricoxib is to be administered in a daily dose of between 20 and 120 mg of the active ingredient. Preferably, COX 189 is to be administered in a daily dose of between 100 and 800 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a COX-2 inhibitor, preferably chosen from the group consisting of valdecoxib, rofecoxib, parecoxib, etoricoxib, COX 189, celecoxib and ABT-963, preferably parecoxib,

etoricoxib or COX 189, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is parecoxib, preferably provided in a unitary dose of between 20 and 80 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is etoricoxib, preferably provided in a unitary dose of between 20 and 120 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is COX 189, preferably provided in a unitary dose of between 100 and 800 mg of the active ingredient.

<u>25: combination therapy with a COX-inhibiting nitric oxide donator (CINOD) compound</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a COX-inhibiting nitric oxide donator (CINOD) compound, are pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a COX-inhibiting nitric oxide donator (CINOD) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said COX-inhibiting nitric oxide donator (CINOD) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said COX-inhibiting nitric oxide donator (CINOD) compound is chosen from the group consisting of AZD4717 and AZD3582 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, AZD3582 is to be administered in a daily dose ranging between 93.75 and 750 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a COX-inhibiting nitric oxide donator (CINOD), preferably chosen from the group consisting of AZD4717 and AZD3582 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-inhibiting nitric oxide donator (CINOD) is AZD3582, preferably provided in a unitary dose of between 93.75 and 750 mg of the active ingredient.

<u>26: combination therapy with a CRF1 (corticoid-releasing factor receptor 1) antagonist</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a CRF1 (Corticotropin-Releasing Factor receptor 1) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders,

personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said CRF1 antagonist compound is chosen from the group consisting of R121919, NBI-34041, elzasonan, CP-448,187, CP-154-526, AAG 561 and 723620, preferably R121919, elzasonan or AAG 561, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, R121919 is to be administered in a daily dose of between 5 and 80 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a CRF1 antagonist, preferably chosen from the group consisting of R121919, NBI-34041, elzasonan, CP-448,187, CP-154-526, AAG 561 and 723620, preferably R121919, elzasonan or AAG 561, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said CRF1 antagonist is R121919, preferably provided in a unitary dose of between 5 and 80 mg of the active ingredient.

27: combination therapy with a D1 (dopamine 1) receptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a D1 (dopamine 1) receptor agonist, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said D1 receptor agonist compound is DAS-431 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D1 receptor agonist, preferably DAS-431 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

28: combination therapy with D2 (dopamine 2) receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with D2 (dopamine 2) receptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said D2 receptor antagonist compound is chosen from the group consisting of bifeprunox, amisulpride aminosultopride and amisulpride, preferably bifeprunox, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D2 receptor antagonist, preferably chosen from the group consisting of bifeprunox, amisulpride aminosultopride and amisulpride, preferably bifeprunox, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering,

antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

29: combination therapy with D3 (dopamine 3) receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with D3 (dopamine 3) receptor antagonist, are chosen from the group of diseases or disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the

therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said D3 receptor antagonist compound is chosen from the group consisting of BSF-201640 and PD 58491, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D3 receptor antagonist, preferably chosen from the group consisting of BSF-201640 and PD 58491, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related

disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium and Parkinson disease.

30: combination therapy with a DA (dopamine) uptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a DA (dopamine) uptake inhibitor, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a DA uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA uptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a DA uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA uptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said DA uptake inhibitor compound is chosen from the group consisting of safinamide and GBR 12909, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D2 receptor antagonist, preferably chosen from the group consisting of safinamide and GBR 12909, or a pro-drug or an active metabolite thereof, or a

pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

31: combination therapy with an dopamine (receptor) agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an dopamine (receptor) agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders and problems related to abuse or neglect,, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said

dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said dopamine (receptor) agonist compound is chosen from the group consisting of sumanirole, SLV 308, sarizotan, S32504, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation), pramipexole, DAB452, cabergoline, bromocriptine, alaptide amantadine, bromocriptine, cabergoline lisuride and pergolide, preferably sumanirole, rotigotine (preferably a Once-a-Day Transdermal Patch), pergolide or ropinirole HCL (preferably controlled-release formulation), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, sumanirole is to be administered in a daily dose of between 4 and 16 mg of the active ingredient. Preferably, rotigotine (Once-a-Day Transdermal Patch) is to be administered in a daily dose of between 4.5 and 13.5 mg of the active ingredient. Preferably, ropinirole HCL (controlled-release formulation) is to be administered in a daily dose of between 0.75 and 24 mg of the active ingredient. Preferably, pergolide is to be administered in a daily dose of between 0.5 and 10 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a dopamine (receptor) agonist, preferably chosen from the group consisting of sumanirole, SLV 308, sarizotan, S32504, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation), pramipexole, DAB452, cabergoline, bromocriptine, alaptide amantadine, bromocriptine, cabergoline lisuride and pergolide, more preferably sumanirole, rotigotine (preferably a

Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation) or pergolide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is sumanirole, preferably provided in a unitary dose of between 4 and 16 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is rotigotine (Once-a-Day Transdermal Patch), preferably provided in a unitary dose of between 4.5 and 13.5 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is ropinirole HCL (controlled-release formulation), preferably provided in a unitary dose of between 0.75 and 24 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is pergolide, preferably provided in a unitary dose of between 0.5 and 10 mg of the active ingredient.

32: combination therapy with a compound activating ERK (extracellular signal-related kinase)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound that activates ERK (extracellular signal-related kinase), are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound that activates ERK (extracellular signal-related kinase) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound that activates ERK (extracellular signal-related kinase), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound that activates ERK (extracellular signal-related kinase) is CPI-1189 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, CPI-1189 is to be administered in a daily dose of between 50 and 100 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound that activates ERK (extracellular signal-related kinase), preferably CPI-1189 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound that activates ERK (extracellular signal-related kinase) is CPI-1189, preferably provided in a unitary dose of between 50 and 100 mg of the active ingredient.

33: combination therapy with a GABA (gamma-aminobutyric acid) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA (gamma-aminobutyric acid) agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders...

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,

dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA agonist compound is nefiracetam or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA agonist, preferably nefiracetam or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

34: combination therapy with a GABA-A agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA-A (gamma-aminobutyric acid receptor A) agonist compound, are sleep disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of sleep disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate

from or prior to the administration of a GABA-A agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-A agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA-A agonist compound is gaboxadol or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, gaboxadol is to be administered in a daily dose of between 5 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an GABA-A agonist, preferably gaboxadol or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of sleep disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A agonist is Gaboxadol, preferably provided in a unitary dose of between 5 and 20 mg of the active ingredient.

35: combination therapy with a GABA-A modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA-A (gamma-aminobutyric acid receptor A) modulator compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious

disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA-A modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-A modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA-A modulator compound is chosen from the group consisting of zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), SL 65.1498, SEP174559, pagoclone, NGD 96-3, indiplon, eszopiclone, CP-730,330 (NGD 96-3) and ocinaplon, preferably zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), pagoclone, NGD 96-3, indiplon or eszopiclone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, zolpidem MR sustained-release version is to be administered in a daily dose of between 10 and 20 mg of the active ingredient. Preferably, zaleplon extended-release is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient. Preferably, pagoclone is to be administered in a daily dose ranging between 7.5 and 60 mg of the active ingredient. Preferably, indiplon is to be administered in a daily dose of between 10 and 20 mg of the active ingredient. Preferably, eszopiclone is to be administered in a daily dose of between 2 and 3 mg of the active ingredient. Preferably, ocinaplon is to be administered in a daily dose of between 10 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA-A modulator, preferably chosen from the group consisting of zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), SL 65.1498, SEP174559, pagoclone, NGD 96-3, indiplon, eszopiclone, CP-730,330 (NGD 96-3) and ocinaplon, preferably zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), pagoclone, NGD 96-3, indiplon or eszopiclone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental

disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is zolpidem MR sustained-release version, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is zaleplon extended-release, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is Pagoclone, preferably provided in a unitary dose of between 7.5 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is indiplon, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is eszopiclone, preferably provided in a unitary dose of between 2 and 3 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is ocinaplon, preferably provided in a unitary dose of between 10 and 60 mg of the active ingredient.

36: combination therapy with a GABA-B antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA-B (gamma-aminobutyric acid receptor B) antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA-B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA-B antagonist compound is AVE 7398 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA-B antagonist, preferably AVE 7398 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform

disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

37: combination therapy with a Glial-cell Line Derived Neurotrophic Factor compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a Glial-cell Line Derived Neurotrophic Factor compound, is Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a Glial-cell Line Derived Neurotrophic Factor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said Glial-cell Line Derived Neurotrophic Factor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said Glial-cell Line Derived Neurotrophic Factor compound is GDNF or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, GDNF is to be administered in a daily dose ranging between 3.75 and 30 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a Glial-cell Line Derived Neurotrophic Factor, preferably GDNF or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said Glial-cell Line Derived Neurotrophic Factor is GDNF, preferably provided in a unitary dose of between 3.75 and 30 mg of the active ingredient.

38: combination therapy with a glucocorticoid synthesis inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a glucocorticoid synthesis inhibitor compound, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glucocorticoid synthesis inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glucocorticoid synthesis inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glucocorticoid synthesis inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glucocorticoid synthesis inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said glucocorticoid synthesis inhibitor compound is metyrapone or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a glucocorticoid synthesis inhibitor, preferably metyrapone or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

39: combination therapy with a glutamate receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a glutamate receptor antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glutamate receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glutamate receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glutamate receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glutamate receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said glutamate receptor antagonist compound is LY354740 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a glutamate receptor antagonist, preferably LY354740 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

<u>40: combination therapy with an GPCR (G-protein-coupled receptor) modulator</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an GPCR (G-protein-coupled receptor) modulator, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GPCR modulator compound to augment the therapeutic effect or to provide a faster

onset of the therapeutic effect of said GPCR modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GPCR modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GPCR modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said GPCR modulator compound is R1204 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GPCR modulator, preferably R1204 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

41: combination therapy with an GR (glucocorticoid receptor) antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an GR (glucocorticoid receptor) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment

disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said GR antagonist compound is chosen from the group consisting of ORG 34517/34850 and mifepristone, preferably mifepristone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, mifepristone is to be administered in a daily dose of between 600 and 1200 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GR antagonist, preferably chosen from the group consisting of ORG

34517/34850 and mifepristone, preferably mifepristone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GR antagonist is Mifepristone, preferably provided in a unitary dose of between 600 and 1200 mg of the active ingredient.

42: combination therapy with a histamine H3-receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a histamine H3-receptor antagonist, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized

in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a histamine H3-receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said histamine H3-receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said histamine H3-receptor antagonist compound is chosen from the group of compounds consisting of ABT-834 and ABT-239, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a histamine H3-receptor antagonist, preferably chosen from the group consisting of ABT-834 and ABT-239 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

43: combination therapy with a hormonal substance

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a hormonal substance, are chosen from the group of diseases or disorders consisting of premenstrual syndrome and sexual and gender identity disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of premenstrual syndrome and sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable

salt thereof is administered simultaneously with, separate from or prior to the administration of a hormonal substance to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said hormonal substance, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said hormonal substance is chosen from the group consisting of a testosterone transdermal spray, a testosterone gel, a female testosterone patch, synthetic conjugated estrogen A, methyltestosterone, a estrogens/methyltestosterone and a drosiperone/ethinyl estradiol composition, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said hormonal substance is synthetic conjugated estrogen A and is to be administered in a daily dose ranging between 0.075 and 0.6 mg of the active ingredient. More preferably, said hormonal substance is a drosiperone/ethinyl estradiol composition and is to be administered as a daily dose in tablets, preferably comprising 3mg drosiperone and 0.02 mg ethinyl estradiol of the active ingredients, respectively.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and
(b) a hormonal substance, preferably chosen from the group consisting of a testosterone transdermal spray, a testosterone gel, a female testosterone patch, synthetic conjugated estrogen A, methyltestosterone, a estrogens/methyltestosterone and a drosiperone/ethinyl estradiol composition, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of premenstrual syndrome and sexual and gender identity disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said hormonal substance is synthetic conjugated estrogen A, preferably provided in a unitary dose of between 0.075 and 0.6 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient

and wherein said hormonal substance is a drosiperone/ethinyl estradiol composition, preferably provided in tablets comprising a unitary dose of 3mg drosiperone and 0.02 mg ethinyl estradiol of the active ingredients, respectively.

44: combination therapy with a compound which increases brain concentrations of 5-HT

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which increases brain concentrations of 5-HT (serotonin), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases brain concentrations of 5-HT (serotonin), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to

augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases brain concentrations of 5-HT (serotonin), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which increases brain concentrations of 5-HT (serotonin) is chosen from the group consisting of triptosine, tramadol, SP 186, PMD 145 and KW 6055, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which increases brain concentrations of 5-HT (serotonin), preferably chosen from the group consisting of triptosine, tramadol, SP 186, PMD 145 and KW 6055, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

45: combination therapy with a compound which increases insulin sensitivity

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which increases insulin sensitivity, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases insulin sensitivity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases insulin sensitivity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which increases insulin sensitivity is rosiglitazone maleate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which increases insulin sensitivity, preferably rosiglitazone maleate or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

<u>46: combination therapy with a compound inhibiting the mixed lineage kinase family</u>

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy

with a compound which is an inhibitor of the mixed lineage kinase family is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is an inhibitor of the mixed lineage kinase family to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is an inhibitor of the mixed lineage kinase family, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which is an inhibitor of the mixed lineage kinase family is CEP-1347 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is an inhibitor of the mixed lineage kinase family, preferably CEP-1347 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

47: combination therapy with an interleukin-1 beta converting enzyme inhibitor compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an interleukin-1 beta converting enzyme inhibitor compound, is a pain disorder.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an interleukin-1 beta converting enzyme inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said interleukin-1 beta converting enzyme inhibitor compound, further

characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said interleukin-1 beta converting enzyme inhibitor is pralnacasan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an interleukin-1 beta converting enzyme inhibitor, preferably pralnacasan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a pain disorder,.

48: combination therapy with a levodopa/decarboylase inhibitor compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a levodopa/decarboylase inhibitor compound, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a levodopa/decarboylase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said levodopa/decarboylase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said levodopa/decarboylase inhibitor compound is levodopa/carbidopa, levodopa/benserazide, etilevodopa/carbidopa or etilevodopa/benserazide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. According to a further preferred embodiment, the invention relates to the use as described above, wherein said levodopa/decarboylase inhibitor compound is (etl)levodopa/carbidopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-

drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably said levodopa/decarboylase inhibitor compound is levodopa/carbidopa and is to be administered in a dose ranging between 2000 mg/ 50 mg and 100 mg/ 10 mg of the active ingredients. Preferably said entacapone is to be administered in a dose ranging between 1000 mg/ 50 mg, more preferably between 500 mg/ 100 mg, and most preferably 200 mg of the active ingredients per day.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a levodopa/decarboylase inhibitor compound, preferably levodopa/carbidopa, levodopa/ benserazide, etilevodopa/carbidopa or etilevodopa/benserazide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease. The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a levodopa/decarboylase inhibitor compound, preferably is (eti)levodopa/carbidopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.
The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboylase inhibitor compound is levodopa/carbidopa, preferably provided in a unitary dose of between 100 mg and 10 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboylase inhibitor compound is levodopa/carbidopa or etilevodopa/ carbidopa in combination with entacapone, of which the latter is preferably provided in a unitary dose of between 500 mg and 100 mg of the active ingredient.

<u>49: combination therapy with a lipid-DNA complex</u>

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a lipid-DNA complex, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of lipid-DNA complex to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said lipid-DNA complex, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said lipid-DNA complex is GR213487B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a lipid-DNA complex, preferably GR213487B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

<u>50: combination therapy with a monoamine oxidase (MAO) reuptake inhibitor</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase (MAO) reuptake inhibitor, are chosen from the group of diseases or disorders consisting of substance related disorders and attention-deficit disorders (ADHD).

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of non-cognitive mental disease or disorder which are substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor compound, further characterized in that

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention-deficit disorders (ADHD), characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase (MAO) reuptake inhibitor compound is NS 2359 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase (MAO) reuptake inhibitor, preferably NS 2359 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of substance related disorders and attention-deficit disorders (ADHD).

51: combination therapy with a MAO-A and a MAO-B reuptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor, wherein said disorders are attention-deficit disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention-deficit disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with,

separate from or prior to the administration of a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound is SPD473 or a pro-drug or an active metabolite thereof, or a pharma-ceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor, preferably SPD473 or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of attention-deficit disorders.

52: combination therapy with a monoamine oxidase B (MAO-B) inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase B (MAO-B) inhibitor, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, characterized in that pipamperon or said

pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase B (MAO-B) inhibitor compound is chosen from the group consisting of selegiline, rasagiline (TVP-1012) and EmSam (transdermal selegiline), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said monoamine oxidase B (MAO-B) inhibitor is selegiline and is to be administered in a daily dose ranging between 5 and 10 mg of the active ingredient. More preferably, said monoamine oxidase B (MAO-B) inhibitor is rasagiline (TVP-1012) and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase B (MAO-B) inhibitor, preferably chosen from the group consisting of selegiline, rasagiline (TVP-1012) and EmSam (transdermal selegiline), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said monoamine oxidase B (MAO-B) inhibitor is selegiline, preferably provided in a unitary dose of between 5 and 10 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said monoamine oxidase B (MAO-B) inhibitor is rasagiline (TVP-1012), preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

<u>53: combination therapy with a monoamine oxidase B (MAO-B) reuptake inhibitor</u>

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase B (MAO-B) reuptake inhibitor, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) reuptake inhibitor to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) reuptake inhibitor, further characterized in that

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said monoamine oxidase B (MAO-B) reuptake inhibitor is safinamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase B (MAO-B) reuptake inhibitor, preferably safinamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

54: combination therapy with a melanocortin-4 (MC4) receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a melanocortin-4 (MC4) receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanocortin-4 (MC4) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanocortin-4 (MC4) receptor

antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanocortin-4 (MC4) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanocortin-4 (MC4) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melanocortin-4 (MC4) receptor antagonist compound is MCL0129, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melanocortin-4 (MC4) receptor antagonist compound, preferably MCL0129 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

55: combination therapy with a MCH receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a melanin concentrating hormone (MCH) receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity

disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanin concentrating hormone (MCH) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanin concentrating hormone (MCH) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanin concentrating hormone (MCH) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanin concentrating hormone (MCH) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melanin concentrating hormone (MCH) receptor antagonist compound is SNAP-7941 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melanin concentrating hormone (MCH) receptor antagonist compound, preferably SNAP-7941 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

56: combination therapy with a melatonin receptor (MT) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a melatonin receptor (MT) agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist

compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melatonin receptor (MT) agonist compound is chosen from the group consisting of ramelteon and agomelatine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said melatonin receptor (MT) agonist compound is agomelatine and is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melatonin receptor (MT) agonist compound, preferably ramelteon or agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said melatonin receptor (MT) agonist compound is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

57: combination therapy with a metabotropic glutamate receptor (MgluR) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a metabotropic glutamate receptor (MgluR) agonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a metabotropic glutamate receptor (MgluR) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said metabotropic glutamate receptor (MgluR) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a metabotropic glutamate receptor (MgluR) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said metabotropic glutamate receptor (MgluR) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said metabotropic glutamate receptor (MgluR) agonist compound is PRE703 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a metabotropic glutamate receptor (MgluR) agonist, preferably PRE703 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

58: combination therapy with a compound mimicking the effect of nerve growth factor (NGF)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which mimics the effect of nerve growth factor (NGF), are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which mimics the effect of nerve growth factor (NGF) is xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said compound which mimics the effect of nerve growth factor (NGF) is xaliproden and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which mimics the effect of nerve growth factor (NGF), preferably xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound which mimics the effect of nerve growth factor (NGF) is xaliproden, preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

59: combination therapy with a muscarinic receptor partial agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a muscarinic receptor partial agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a muscarinic receptor partial agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said muscarinic receptor partial agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said muscarinic receptor partial agonist compound is sevimeline or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a muscarinic receptor partial agonist compound, preferably sevimeline or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

60: combination therapy with a selective nor-adrenaline re-uptake inhibitor (NARI) compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective nor-adrenaline re-uptake inhibitor (NARI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline receptor inhibitor (NARI) compound to augment the therapeutic

effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline re-uptake inhibitor (NARI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is chosen from the group consisting of reboxetine, atomoxetine hydrochloride, A 75200, 155U88, (S)-A 75200, tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine and milnacipran or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective nor-adrenaline re-uptake inhibitor (NARI) compound is reboxetine and is to be administered in a daily dose ranging between 8 and 12 mg of the active ingredient. More preferably, said selective nor-adrenaline re-uptake inhibitor (NARI) compound is atomoxetine hydrochloride and is to be administered in a daily dose ranging between 40 and 100 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective nor-adrenaline re-uptake inhibitor (NARI) compound, preferably chosen from the group consisting of reboxetine, atomoxetine hydrochloride, A 75200, 155U88, (S)-A 75200, tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine and milnacipran, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental

disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is reboxetine, preferably provided in a unitary dose of between 8 and 12 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is atomoxetine hydrochloride, preferably provided in a unitary dose of between 40 and 100 mg of the active ingredient.

61: combination therapy with a NaSSA compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a noradrenergic/specific serotonergic antidepressant (NaSSA) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse

or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said noradrenergic/specific serotonergic antidepressant (NaSSA) compound is ORG 4420 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a noradrenergic/specific serotonergic antidepressant (NaSSA) compound, preferably ORG 4420 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

62: combination therapy with a selective NDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor

(NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound is GW353162 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound is GW353162 and is to be administered in a daily dose ranging between 20 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, preferably GW353162 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia,

vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound is GW353162, preferably provided in a unitary dose of between 20 and 60 mg of the active ingredient.

63: combination therapy with a compound which is a neuroimmunophilin ligand

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which is a neuroimmunophilin ligand, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a neuroimmunophilin ligand to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a neuroimmunophilin ligand, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said a compound which is a neuroimmunophilin ligand is GPI 1485 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said a compound which is a neuroimmunophilin ligand is GPI 1485 and is to be administered in a daily dose ranging between 200 and 1000 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a neuroimmunophilin ligand, preferably GPI 1485 or a pro-

drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said a compound which is a neuroimmunophilin ligand is GPI 1485, preferably provided in a unitary dose of between 200 and 1000 mg of the active ingredient.

64: combination therapy with a neuromodulator compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neuromodulator compound, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neuromodulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neuromodulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said neuromodulator compound is adenosine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neuromodulator compound, preferably adenosine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

65: combination therapy with a neurotensin receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neurotensin receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to

be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said neurotensin receptor antagonist compound is SR 48692 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neurotensin receptor antagonist compound is SR 48692 and is to be administered in a daily dose ranging between 90 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neurotensin receptor antagonist compound, preferably SR 48692 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said neurotensin receptor antagonist compound is SR 48692, preferably provided in a unitary dose of between 90 and 300 mg of the active ingredient.

66: combination therapy with nerve growth factor (NGF) gene therapy

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with nerve growth factor (NGF) gene therapy, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nerve growth factor (NGF) gene therapy, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of nerve growth factor (NGF) gene therapy, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound useful in nerve growth factor (NGF) gene therapy, preferably xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

It should be understood that "nerve growth factor gene therapy" is well known in the art, and the compounds, for instance nucleic acids used in nerve growth factor gene therapy are well described (see e.g. Tuszynski *et al.*, (2002) Journal of Molecular Neuroscience Volume 19, Issue 1-2, pps. 207-208).

<u>67: combination therapy with a nicotinic acetylcholine receptor antagonist compound</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a nicotinic acetylcholine receptor antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a nicotinic acetylcholine receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic acetylcholine receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic acetylcholine receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic acetylcholine receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said nicotinic acetylcholine receptor antagonist compound is SEP174559 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a nicotinic acetylcholine receptor antagonist compound, preferably SEP174559 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

68: combination therapy with a nicotinic receptor agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a nicotinic receptor agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia,

vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said nicotinic receptor agonist compound is ABT-089, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said nicotinic receptor agonist compound is ABT-089 and is to be administered in a daily dose ranging between 4 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a nicotinic receptor agonist compound, preferably ABT-089 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease,

dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above, wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said nicotinic receptor agonist compound is ABT-089, preferably provided in a unitary dose of between 4 and 40 mg of the active ingredient.

69: combination therapy with a neurokinin 2 receptor (NK2) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neurokinin 2 receptor (NK2) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said neurokinin 2 receptor (NK2) antagonist compound is saredutant or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neurokinin 2 receptor (NK2) antagonist compound is saredutant and is to be administered in a daily dose ranging between 25 and 200 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neurokinin 2 receptor (NK2) antagonist compound, preferably saredutant or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said neurokinin 2 receptor (NK2) antagonist compound is saredutant, preferably provided in a unitary dose of between 25 and 200 mg of the active ingredient.

70: combination therapy with a neurokinin 3 receptor (NK3) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neurokinin 3 receptor (NK3) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said neurokinin 3 receptor (NK3) antagonist compound is talnetant or osanetant, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neurokinin 3 receptor (NK3) antagonist compound is talnetant and is to be administered in a daily dose ranging between 1.5 and 12 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neurokinin 3 receptor (NK3) antagonist compound, preferably talnetant or osanetant, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient

and wherein said neurokinin 3 receptor (NK3) antagonist compound is talnetant, preferably provided in a unitary dose of between 1.5 and 12 mg of the active ingredient.

71: combination therapy with an N-Methyl-D-aspartate (NMDA) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an N-Methyl-D-aspartate (NMDA) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound; further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said N-Methyl-D-aspartate (NMDA) antagonist compound is chosen from the group consisting of SEP174559, memantine, delucemine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said N-Methyl-D-aspartate (NMDA) antagonist compound is memantine and is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an N-Methyl-D-aspartate (NMDA) antagonist compound, preferably chosen from the group consisting of SEP174559, memantine, delucemine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said N-Methyl-D-aspartate (NMDA) antagonist compound is memantine, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.

72: combination therapy with a non-steroidal anti-inflammatory drug

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a non-steroidal anti-inflammatory drug, is a pain disorder or Alzheimer Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a non-steroidal anti-inflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disease, such as Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered

simultaneously with, separate from or prior to the administration of a non-steroidal anti-inflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said a non-steroidal anti-inflammatory drug is chosen from the group consisting of piroxicam , MX-1094, meloxicam and flurizan (pure R-enantiomer form of flurbiprofen), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a non-steroidal anti-inflammatory drug, preferably chosen from the group consisting of piroxicam, MX-1094, meloxicam and flurizan (pure R-enantiomer form of flurbiprofen), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a pain disorder or Alzheimer Disease .

73: combination therapy with an opoid antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an opoid antagonist compound, are substance related disorders.

It will be appreciated that the terms "opoid" and "opioid" may be used interchangeably.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a opoid antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said opoid antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said opoid antagonist compound is naltrexone, preferably as a depot formulation, more preferably in the form of microcapsules, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, said naltrexone is to be administered in the form of a depot, preferably a depot of microcapsules comprising a daily dose of between 192 and 384 mg.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a opoid antagonist, preferably naltrexone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of substance related disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said opoid antagonist compound is naltrexone, preferably provided in a unitary dose of between 192 and 384 mg of the active ingredient.

74: combination therapy with an opoid agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an opoid agonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and

problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an opoid agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said opoid agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said opoid agonist compound is chosen from the group consisting of siramesine, E-5842 and cyclazocine, preferably siramesine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an opoid agonist compound, preferably chosen from the group consisting of siramesine, E-5842 and cyclazocine, preferably siramesine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

75: combination therapy with a phosphodiesterase-4 (PDE4) inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a phosphodiesterase-4 (PDE4) inhibitor compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob

Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound d to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said phosphodiesterase-4 (PDE4) inhibitor compound is chosen from the group consisting of ND1251 and MEM 1917 (R1497), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a phosphodiesterase-4 (PDE4) inhibitor antagonist compound, preferably chosen from the group consisting of ND1251 and MEM 1917 (R1497), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

<u>76: combination therapy with a peptidic compound</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a peptidic compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome,

somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group

of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said peptidic compound is chosen from the group consisting of secretin, PT-141, INN 00835 and beta sheet breaker peptide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said peptidic compound is secretin and is to be administered in a daily dose ranging between 0.2 and 0.4 mg/kg of the active ingredient. More preferably, said peptidic compound is INN 00835 and is to be administered in a daily dose ranging between 18 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a peptidic compound, preferably chosen from the group consisting of secretin, PT-141, INN 00835 and beta sheet breaker peptide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition,

substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said peptidic compound is secretin, preferably provided in a unitary dose of 0.2 and 0.4 mg/kg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said peptidic compound is INN 00835, preferably provided in a unitary dose of 18 and 160 mg of the active ingredient.

77: combination therapy with a phospholipase A2 inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a phospholipase A2 inhibitor compound which has caspase inhibitor activity, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect,, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the

administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said phospholipase A2 inhibitor compound which has caspase inhibitor activity is chosen from the group consisting of LAX-101a, LAX-101b and LAX-101c, preferably LAX-101a, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a phospholipase A2 inhibitor compound which has caspase inhibitor activity, preferably chosen from the group consisting of LAX-101a, LAX-101b and LAX-101c, more

preferably LAX-101a, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

78: combination therapy with a compound which is a prodrug of uridine

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which is a prodrug of uridine, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a prodrug of uridine to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a prodrug of uridine, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a prodrug of uridine to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a prodrug of uridine, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which is a prodrug of uridine is RG2133 (triacetyluridine) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a prodrug of uridine, preferably RG2133 (triacetyluridine) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

<u>79: combination therapy with prostaglandin E1 compound</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with prostaglandin E1 compound, are sexual and gender identity disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate

from or prior to the administration of a prostaglandin E1 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said prostaglandin E1 compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said prostaglandin E1 is alprostadil or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said prostaglandin E1 compound is alprostadil, preferably in the form of cream or gel, preferably a topical gel, and is to be administered in a daily dose ranging between 50 and 300 microgram per application of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a prostaglandin E1 compound, preferably alprostadil or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of sexual and gender identity disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said prostaglandin E1 compound is alprostadil, preferably provided in the form of a cream or gel, preferably a topical gel, wherein a unitary dose comprises between 50 and 300 microgram of the active ingredient per application.

<u>80: combination therapy with a compound protecting dopaminergic and cholinergic neurons</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which protects dopaminergic and cholinergic neurons, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic

disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which protects dopaminergic and cholinergic neurons is SR 57667 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which protects dopaminergic and cholinergic neurons, preferably SR 57667 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

81: combination therapy with a psychostimulant

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a psychostimulant, are chosen from the group of diseases or disorders consisting of sleep disorders, attention-deficit disorders and substance-related disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of sleep disorders, attention-deficit disorders and substance-related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a psychostimulant to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said psychostimulant, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said psychostimulant is chosen from the group consisting of SPD 503, r-modafinil and modafinil, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said psychostimulant is SPE 503, more preferably said psychostimulant is modafinil and is to be administered in a daily dose ranging between 200 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a psychostimulant, preferably chosen from the group consisting of SPD 503, r-modafinil and modafinil, more preferably said SPC 503 or modafinil or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of sleep disorders, attention-deficit disorders and substance-related disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said psychostimulant is modafinil, preferably provided in a unitary dose of between 200 and 600 mg of the active ingredient.

<u>82: combination therapy with a compound which is a Reversible Inhibitor of Mono-Amine oxydase A (RIMA)</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is chosen from the group consisting of toloxatone, RS 8359, moclobemide, cimoxatone, caroxazone (F.I 6654) and befloxatone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is befloxatone and is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), preferably chosen from the group consisting of toloxatone, RS 8359, moclobemide, cimoxatone, caroxazone (F.I 6654) and befloxatone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality

disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is befloxatone, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

83: combination therapy with a compound which modulates SCT-11

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which modulates SCT-11 (i.e. SCT-11 is a G protein-coupled receptor), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which modulates SCT-11 to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which modulates SCT-11, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which modulates SCT-11 to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which modulates SCT-11, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which modulates SCT-11 is SNEC-2 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which modulates SCT-11, preferably SNE-2 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

<u>84: combination therapy with a serotonin/dopamine antagonist compound (SDA)</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a serotonin/dopamine antagonist compound (SDA), are chosen from the group of diseases or disorders consisting of ~~mood disorders~~, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound,

further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said serotonin/dopamine antagonist compound is chosen from the group consisting of zotepine, ziprasidone, SM-13496, SL 91.0177, sertindole, S-18327, risperidone, quetiapine fumarate (preferably sustained release formulation), quetiapine fumarate (preferably granules), quetiapine, perospirone, paliperidone, olanzapine, ocaperidone, LU 31-131, iloperidone, clozapine, BSF-190555, blonanserin, bifeprunox, asenapine and aripiprazole, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said serotonin/dopamine antagonist compound is chosen from the group consisting of SL 91.0177, sertindole, perospirone, paliperidone, blonanserin, bifeprunox and asenapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said serotonin/dopamine antagonist compound is sertindole and is to be administered in a daily dose ranging between 12 and 24 mg of the active ingredient. More preferably, said serotonin/dopamine antagonist compound is paliperidone and is to be administered in a daily dose ranging between 3 and 15 mg of the active ingredient. More preferably, said serotonin/dopamine antagonist compound is asenapine and is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a serotonin/dopamine antagonist compound, preferably chosen from the group consisting of SL 91.0177, sertindole, perospirone, paliperidone, blonanserin, bifeprunox and asenapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is sertindole, preferably provided in a unitary dose of between 12 and 24 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is paliperidone, preferably provided in a unitary dose of between 3 and 15 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is asenapine, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

85: combination therapy with a selective SDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin and dopamine re-uptake inhibitor (SDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),

factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptakeinhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin and dopamine reuptake inhibitor (SDRI) compound is bazinaprine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin and dopamine reuptake inhibitor (SDRI) compound, preferably bazinaprine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

<u>86: combination therapy with a second messenger beta agonist compound</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a second messenger beta agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said second messenger beta agonist compound is chosen from the group consisting of SR 57227, rolipram and eplivanserin, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said second messenger beta agonist compound is rolipram and is to be administered in a daily dose ranging between 1.5 and 3 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a second messenger beta agonist compound, preferably chosen from the group consisting of SR 57227, rolipram and eplivanserin or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for

simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said second messenger beta agonist compound is rolipram, preferably provided in a unitary dose of between 1.5 and 3 mg of the active ingredient.

87: combination therapy with a secretin pancreatic hormone

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a secretin pancreatic hormone, are chosen from the group of diseases or disorders consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the

administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said secretin pancreatic hormone is RG1068 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a secretin pancreatic hormone, preferably RG1068, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive

behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

88: combination therapy with a sigma receptor agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a sigma receptor agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor agonist compound to augment the

therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said sigma receptor agonist compound is VPI-013 (also known as OPC-14523) or PRX-00023, preferably VPI-013 (also known as OPC-14523), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sigma receptor agonist compound, preferably VPI-013 (also known as OPC-14523) or PRX-00023, preferably VPI-013 (also known as OPC-14523), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

89: combination therapy with a sigma receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a sigma receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the

group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect,, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said sigma receptor antagonist compound is chosen from the group consisting of SR 31742 and EMD 68843, or a pro-drug or an active metabolite thereof, or

a pharmaceutically acceptable salt thereof. More preferably, said sigma receptor antagonist compound is EMD 68843 and is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sigma receptor antagonist compound, preferably chosen from the group consisting of SR 31742 and EMD 68843, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said sigma receptor antagonist compound is EMD 68843, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.

90: combination therapy with a selective SNDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition,

substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to

head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound is selected from the group consisting of NS 2330; McN 5652; DOV 216,303 and DOV 21,947; more preferably NS 2330 or DOV 216,303; or a pro-drug or an active metabolite thereof; or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, preferably selected from the group consisting of NS 2330; McN 5652; DOV 216,303 and DOV 21,947, more preferably NS 2330 or DOV 216,303, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

91: combination therapy with a selective SNRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor

(SNRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is selected from the group consisting of venlafaxine, tomoxetine, tandamine, talsupram, talopram, nefazodone, milnacipran, LY 113.821, duloxetine, desvenlafaxine and amoxapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is chosen from the group consisting of venlafaxine, tomoxetine, milnacipran, duloxetine and desvenlafaxine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is venlafaxine and is to be administered in a daily dose ranging between 75 and 300 mg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is tomoxetine and is to be administered in a daily dose ranging between 0.475 and 3.8 mg/kg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is milnacipran and is to be administered in a daily dose ranging between 50 and 200 mg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is duloxetine and is to be administered in a daily dose ranging between 40 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, preferably selected from the group consisting of venlafaxine, tomoxetine, tandamine, talsupram, talopram, nefazodone, milnacipran, LY 113.821, duloxetine, desvenlafaxine and amoxapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is venlafaxine, preferably provided in a unitary dose of between between 75 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is tomoxetine, preferably provided in a unitary dose of between 0.475 and 3.8 mg/kg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is milnacipran, preferably provided in a unitary dose of between 50 and 200 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is duloxetine, preferably provided in a unitary dose of between 40 and 60 mg of the active ingredient.

92: combination therapy with a selective serotonin re-uptake inhibitor (SSRI) compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin re-uptake inhibitor (SSRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin re-uptake inhibitor (SSRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin re-uptake inhibitor (SSRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin re-uptake inhibitor (SSRI) compound is selected from the group consisting of YM 992, VPI-013 (also known as OPC-14523), sertraline, paroxetine, LY 214.281, LU AA-21-004, Lu-35-138, litoxetine, ifoxetine, fluvoxamine (controlled release formulation), fluvoxamine, fluoxetine, femoxetine, escitalopram, EMD 68843, cyanodothepine, citalopram, venlafaxine, milnacipran, duloxetine, ericlamine and ademethionine (preferably s-adenosylmethionine), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is chosen from the group consisting of litoxetine, fluvoxamine (controlled release formulation) and escitalopram, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is fluvoxamine (controlled release formulation) and is to be administered in a daily dose ranging between 100 and 300 mg of the active ingredient. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is escitalopram and is to be administered in a daily dose ranging between 10 and 20 mg of the active ingredient. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is citalopram and is to be administered in a daily dose ranging between 10 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin re-uptake inhibitor (SSRI) compound, preferably selected from the group consisting of YM 992, VPI-013 (also known as OPC-14523), sertraline, paroxetine, LY 214.281, LU AA 21-004, Lu 35-138, litoxetine, ifoxetine, fluvoxamine (controlled release formulation), fluvoxamine, fluoxetine, femoxetine, escitalopram, EMD 68843, cyanodothepine, citalopram, venlafaxine, milnacipran, duloxetine, cericlamine and ademethionine (preferably s-adenosylmethionine), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is fluvoxamine (controlled release formulation), preferably provided in a unitary dose of between between 100 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is escitalopram, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is citalopram, preferably provided in a unitary dose of between 10 and 40 mg of the active ingredient.

Citalopram or citalopram hydrobromide is a selective serotonin (5-hydroxytryptamine / 5-HT) re-uptake inhibitor (SSRI) and is the conventional name given for the compound of the formula (RS)-1-[3-(dimethylamino)propyl]-1-(p-flurophenyl)-5-phthalancarbonitrile-hydro-bromide. According to an embodiment, a daily doses of active ingredient of SSRI, preferably citalopram, ranges between 10 and 40 mg per day. Preferably, daily doses of active ingredient ranging between 20 and 30 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.

Fluvoxamine or fluvoxamine maleate (luvox, fevarin) is a selective serotonin (5-HT) re-uptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl) oxime maleate (1:1).

According to an embodiment, a daily dose of active ingredient of fluvoxamine in a controlled release mode ranges between 100 and 300 mg per day. Preferably, daily doses of active ingredient ranging between 150 and 200 mg per day are administered in a controlled release mode. More preferably, a daily dose of 100, 150, 200, 250 or 300 mg per day is administered by controlled release.

93: combination therapy with a substance P receptor (NK1) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a substance P receptor (NK1) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a substance P receptor (NK1) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a substance P receptor (NK1) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said substance P receptor (NK1) antagonist compound is chosen from the group consisting of vestipitant, TAK-637, R673, GW823296, GW679769, GW597599, CP-122.721, aprepitant, 823296 and 679769, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said substance P receptor (NK1) antagonist compound is aprepitant and is to be administered in a daily dose ranging between 40 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a substance P receptor (NK1) antagonist compound, preferably chosen from the group consisting of vestipitant, TAK-637, R673, GW823296, GW679769, GW597599, CP-

122.721, aprepitant, 823296 and 679769, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said substance P receptor (NK1) antagonist compound is aprepitant, preferably provided in a unitary dose of between 40 and 160 mg of the active ingredient.

94: combination therapy with a sulfonamide compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a sulfonamide compound, are chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering,

antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said sulfonamide compound is zonisamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said sulfonamide compound is zonisamide and is to be administered in a daily dose ranging between 100 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sulfonamide compound, preferably zonisamide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined

preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said sulfonamide compound is zonisamide, preferably provided in a unitary dose of between 100 and 600 mg of the active ingredient.

95: combination therapy with a tachykinin antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a tachykinin antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of

a tachykinin antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a tachykinin antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said tachykinin antagonist compound is SR 48968 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a tachykinin antagonist compound, preferably SR 48968 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

<u>96: combination therapy with a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493</u>

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, are chosen from the group of

diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

97: combination therapy with a vasopressin 1B receptor (V1B) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a vasopressin 1B receptor (V1B) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating

disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a vasopressin 1B receptor (V1B) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vasopressin 1B receptor (V1B) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a vasopressin 1B receptor (V1B) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vasopressin 1B receptor (V1B) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said vasopressin 1B receptor (V1B) antagonist compound is SSR149415 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a vasopressin 1B receptor (V1B) antagonist compound, preferably SSR149415 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders,

bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

98: combination therapy with a voltage-gated calcium channel α(2)δ subunit modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a voltage-gated calcium channel alpha(2)delta subunit modulator compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a voltage-gated calcium channel alpha(2)delta subunit modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said voltage-gated calcium channel alpha(2)delta subunit modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a voltage-gated calcium channel alpha(2)delta

subunit modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said voltage-gated calcium channel alpha(2)delta subunit modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said voltage-gated calcium channel alpha(2)delta subunit modulator compound is pregabalin or PD-200,390; or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said voltage-gated calcium channel alpha(2)delta subunit modulator compound is pregabalin, and is to be administered in a daily dose ranging between 50 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a voltage-gated calcium channel alpha(2)delta subunit modulator compound, preferably pregabalin or PD-200,390; or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said voltage-gated calcium channel alpha(2)delta subunit modulator compound is pregabalin, preferably provided in a unitary dose of between 50 and 600 mg of the active ingredient.

99: combination therapy with a vomeropherin compound

The mental disorders which ~~can be treated~~ using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a vomeropherin compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual

and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of vomeropherin compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vomeropherin compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said vomeropherin compound is PH94B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) vomeropherin compound, preferably PH94B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

Also, the invention relates in particular to the use as described before, wherein said second compound is chosen from the group consisting of fluvoxamine controlled release,

phenserine tartrate, atomoxetine hydrochloride, bupropion (controlled-release formulation), ropinirole HCL (controlled-release formulation), INN 00835, galantamine (extended release formulation), paliperidone, tomoxetine, aprepitant, rivastigmine tartrate, ORG 34517/34850, sunepitron, sumanirole, milnacipran, idazoxan, xaliproden, SR 58611, befloxatone, litoxetine, tianeptine, agomelatine, SPD 503, flesinoxan, bifeprunox, ramelteon, etilevodopa, rasagiline (TVP-1012) and desvenlafaxine.

Also, the invention relates in particular to the use as described before, wherein said second compound is chosen from the group consisting of galantamine (extended release formulation), R121919, risperidone, paliperidone and R228060 (YKP-10A).

The disclosure of all patents, publications (including published patent publications), and database accession numbers and depository accession numbers referenced in this specification are specifically incorporated herein by reference in their entirety to the same extent as if each such individual patent, publication, and database accession number, and depository accession number were specifically and individually indicated to be incorporated by reference.

The invention, now being generally described, will be more readily understood by reference to the following tables and examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention and are not intended to limit the invention.

Short description of the Tables and Figures

Table 1: In Table 1, the pKi values of test compounds are given for each of the dopamine receptors, 5HT receptors, adrenergic receptors and the histamine1 receptor.

Table 2: Set-up of a clinical trial comprising for treatment groups.

Table 3: Overview of a placebo, active and period controlled clinical trial in a fore-going pipamperon - citalopram treatment in Major Depressive Disorder.

Table 4: POC process for major depressive disorder.

Table 5: Summary of diseases and disorders relative to known psycho-tropics.

Table 6: Overview of Pharmacological grouping, indicating pharmacological profile numbering (column 2), pharmacological profile (column 3), main indication(s) (column 4), name of the compound (column 4), the dose range (column 5), and the company producing or selling said compound (column 6). Compounds indicated by hatching are preferred.

Figure 1: Add-on treatment with pipamperon after treatment with citalopram .

Figure 2: HDRS-17 change from baseline: combo treatment pipamperon as add-on - citalopram vs SNRI (duloxetine) in Major Depression.

Figure 3: Remission rates (HDRS-17 <=7): combo treatment pipamperon as add-on - citalopram vs SNRI (venlafaxine) vs SSRIs vs placebo in Major Depression.

Figure 4: Fore-going treatment during 1-5 days with pipamperon followed with the combination treatment of pipamperon and citalopram.

Figure 5: HDRS-17 change from baseline: combo treatment pipamperon - citalopram with a fore-going treatment of 4 days with pipamperon vs SNRI (duloxetine) in Major Depression.

Figure 6: Remission rates (HDRS-17 <=7): combo pipamperon - citalopram with a fore-going treatment of 4 days with pipamperon vs SNRI (venlafaxine) in Major Depression.

Figure 7: Fore-going treatment during 6-8 days with pipamperon followed with the combination treatment of pipamperon and citalopram.

Figure 8: HDRS-17 change from baseline: combo treatment pipamperon - citalopram with a fore-going treatment of 7 days with pipamperon vs SNRI (duloxetine) in Major Depression.

Figure 9: Fore-going and add-on treatment with pipamperon in MDD.

Figure 10: HDRS-17 change from baseline: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SNRI duloxetine in Major Depression.

Figure 11: Remission rates (HDRS-17 <=7): fore-going and add-on treatment with pipamperon and citalopram in comparison with the SNRI venlafaxine in Major Depression.

Figure 12: Y-BOCS total score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.

Figure 13: Y-BOCS obsession score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.

Figure 14: Y-BOCS compulsion score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.

Figure 15: CGI-severity score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI in panic disorder.

Table 1

	D1	D2	D3	D4	$5HT_{1A}$	$5HT_{1B}$	$5HT_{1D}$	$5HT_{1E}$	$5HT_{1F}$	$5HT_{2A}$	$5HT_{2B}$	$5HT_{2C}$	$5HT_{6}rat$	$5HT_{7}rat$	Alpha1A	Alpha2A	Alpha2B	Alpha2C	Beta1	Beta2	H1
ORG5222	8-9	8-9	8-9	8-9	8-9	8-9	8-9	7-8	0	>9	>9	>9	>9	>9	>9	8-9	>9	7-8	<6	<6	>9
Zotepine	0	8-9	8-9	7-8	6-7	7-8	7-8	6-7	0	8-9	0	0	0	0	0	6-7	8-9	6-7	<6	<6	>9
Fluparoxan	0	<6	<6	<6	6-7	<6	<6	0	0	<6	0	<6	0	0	6-7	8-9	8-9	8-9	0	0	0
Olanzapine	7-8	7-8	7-8	7-8	<6	6-7	6-7	<6	6-7	8-9	8-9	8-9	7-8	6-7	7-8	6-7	6-7	6-7	<6	<6	>9
Clozapine	7-8	6-7	6-7	6-7	6-7	6-7	6-7	6-7	6-7	8-9	8-9	7-8	7-8	7-8	8-9	7-8	7-8	7-8	<6	<6	>9
S16924	0	7-8	7-8	7-8	8-9	0	0	0	0	>9	8-9	7-8	7-8	7-8	8-9	6-7	7-8	6-7	<6	<6	0
S18327	7-8	7-8	6-7	8-9	7-8	0	0	0	0	8-9	0	6-7	0	0	>9	6-7	0	0	0	0	0
Amperozide	6-7	6-7	6-7	8-9	<6	0	0	0	0	8-9	0	<6	0	0	7-8	<6	0	0	0	0	0
GGR218231	<6	7-8	>9	>9	6-7	<6	<6	0	0	>9	<6	<6	0	0	<6	<6	0	0	0	0	0
Sertindole	7-8	8-9	8-9	>9	6-7	7-8	7-8	6-7	6-7	>9	0	8-9	0	0	>9	6-7	6-7	6-7	<6	<6	6-7
MDL100,907	6-7	<6	<6	>9	<6	0	0	0	0	>9	0	7-8	0	0	<6	<6	0	0	0	0	0
Haloperidol	8-9	>9	8-9	8-9	<6	6-7	<6	<6	<6	>9	<6	<6	<6	6-7	8-9	<6	6-7	<6	<6	<6	6-7
Tiospirone	7-8	8-9	>9	8-9	8-9	0	0	0	0	>9	0	8-9	0	0	>9	6-7	0	0	0	0	0
Raciopride	<6	8-9	8-9	<6	<6	0	0	0	0	>9	0	<6	0	0	<6	<6	0	0	0	0	0
Fluspirilene	0	>9	8-9	8-9	7-8	<6	<6	<6	0	>9	0	0	0	0	0	6-7	7-8	7-8	6-7	6-7	7-8
Ocaperidone	7-8	>9	8-9	8-9	7-8	0	0	0	0	>9	0	7-8	0	0	>9	0	0	0	0	0	0
Risperidone	7-8	8-9	7-8	8-9	6-7	8-9	6-7	<6	<6	>9	0	7-8	0	0	>9	7-8	8-9	8-9	<6	<6	7-8
S33084	6-7	7-8	>9	>9	<6	6-7	6-7	0	0	>9	6-7	7-8	0	0	6-7	<6	0	0	0	0	0
L741626	6-7	8-9	7-8	>9	<6	<6	<6	0	0	>9	6-7	<6	0	0	6-7	<6	0	0	0	0	0
Seroquel	6-7	6-7	6-7	>9	6-7	<6	<6	<6	<6	>9	6-7	6-7	0	6-7	7-8	<6	7-8	6-7	<6	<6	8-9
Yohimbine	0	6-7	<6	>9	7-8	6-7	7-8	0	0	>9	0	<6	0	0	6-7	8-9	8-9	>9	<6	<6	0
Ziprasidone	8-9	8-9	7-8	>9	8-9	>9	8-9	6-7	0	>9	8-9	8-9	7-8	8-9	8-9	6-7	7-8	7-8	<6	<6	7-8
Pipamperon	0	6-7	6-7	8-9	<6	6-7	6-7	<6	<6	8-9	0	0	0	0	0	6-7	7-8	6-7	<6	<6	<6

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Table 2

	ACUTE PHASE**						EXTENSION PHASE***										FOLLOW-UP PHASE		
VISITS	V1 Screen	V2 Baseline	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19
Day / Week / Month	min 4 D	D0	D4	D7	W2	W3	W4	W6	W8	W10	W12	W16	W20	W24	M8	M10	M12	W1	W2
TREATMENT GROUP																			
Group Pip Active / D7	A	B	B	C	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	A	A
Group Pip Active / D4	A	B	C	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	A	A
Group Pip Active / D0	A	C	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	A	A
Group Plc Active / D0	A	D	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	A	A
Informed Consent	X																		
NECT*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs / Weight	X													X			X		X
LAB	X													X			X		X
ECG	X													X			X		X
Phys Exam	X																		
Alc/Drugs Screen	X													X			X		X
CGI-S****	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Q-LES-Q*****																			

Treatment regimen:
A: PLC + PLC
B: 2x(PLC+PIP(4mg))/d
C: 2x(CIT(10mg)+PIP(4mg))/d
D: 2x(CIT(10mg)+PLC)/d

*Neuronal E-Clinical Trial = Vesalius Expert Development for this Trial which includes the bottom-up measurement of:

**Entering Acute Phase: only NON-placebo responders as defined by the DSM-IV criteria of efficacy

***Entering Extension Phase: only remittors as defined by the DSM-IV criteria of efficacy

****CGI-S : Clinical Global Impressions-Improvement Scale

*****Q-LES-Q : Quality of Life, Enjoyment and Satisfaction Questionnaire

Table 3

FOREGOING PIPAMPERON - CITALOPRAM TREATMENT IN MAYOR DEPRESSIVE DISORDER A PLACEBO, ACTIVE AND PERIODE CONTROLLED CLINICAL TRIAL																				
	ACUTE PHASE**										EXTENSION PHASE***								FOLLOW-UP PHASE	
VISITS / DAY / WEEK / MONTH	V1 SCREEN	V2 BASELINE	[illegible]	[illegible]	V4 D7	V5 W2	V6 W3	V7 W4	V8 W6	V9 W8	V10 W10	V11 W12	V12 W16	V13 W20	V14 W24	V15 M6	V16 M9	V17 M12	V18 W1	V19 W2
TREATMENT GROUP																				
Group Pip / Active Day [illegible]	PLC/PLC	2x PIP (... mg) [illegible]	[illegible]																PLC/PLC	PLC/PLC
Group [illegible] Active Day [illegible]	PLC/PLC	[illegible]																	PLC/PLC	PLC/PLC
Group Pip Active Day [illegible]	PLC/PLC	2x [illegible]																	PLC/PLC	PLC/PLC
Group Placebo	PLC/PLC	[illegible]																	PLC/PLC	PLC/PLC
[illegible]																				
Informed Consent	X																			
NECT*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs / Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LAB	X	X									X		X		X			X		
ECG	X										X		X		X			X		
Phys Exam	X							X			X		X		X			X		
Alc/Drugs Screening	X										X		X		X			X		
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
****Q-LES-Q	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X

*Neuronal E-Clinical Trial = Vesalius Expert Development for this Trial which includes the bottom-up measurement of:
. In- and exclusioncriteria
. Functional status evaluation
. Medical history
. (Pre-)treatment signs & symptoms
. DSM-IV rules for diagnosis & efficacy
. Rating Scales: HDRS-28, MADRS, HAMA
. Medical resource utulisation
. Pre-trial & Concomittant medication
. Drug administration
. (Seriuos) Adverse events
. Admission to the acute and extension phase of treatment
. Right flow of the trial

**Entering Acute Phase: only NON-placebo responders as defined by the DSM-IV criteria of efficacy

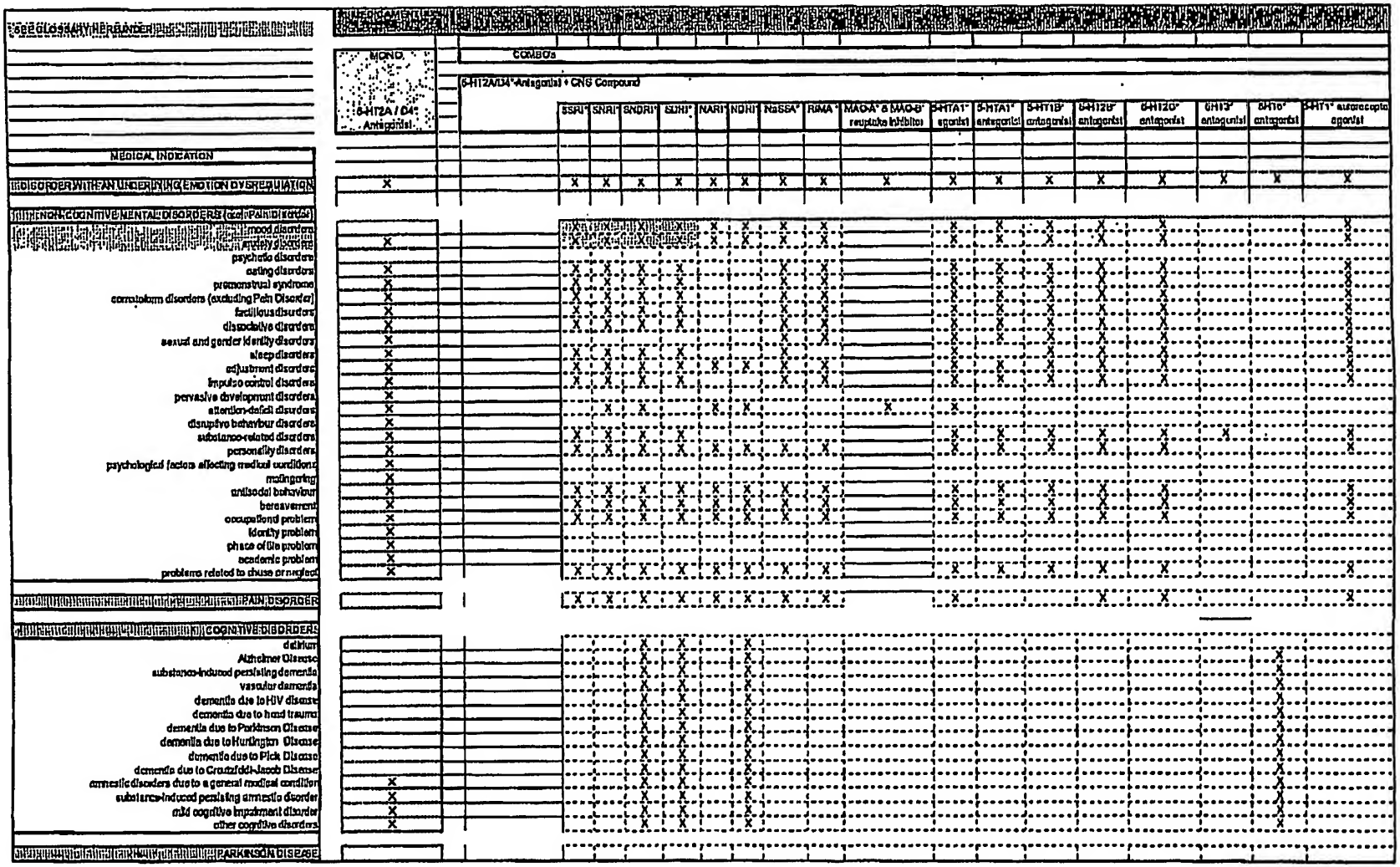
***Entering Extension Phase: only remittors as defined by the DSM-IV criteria of efficacy

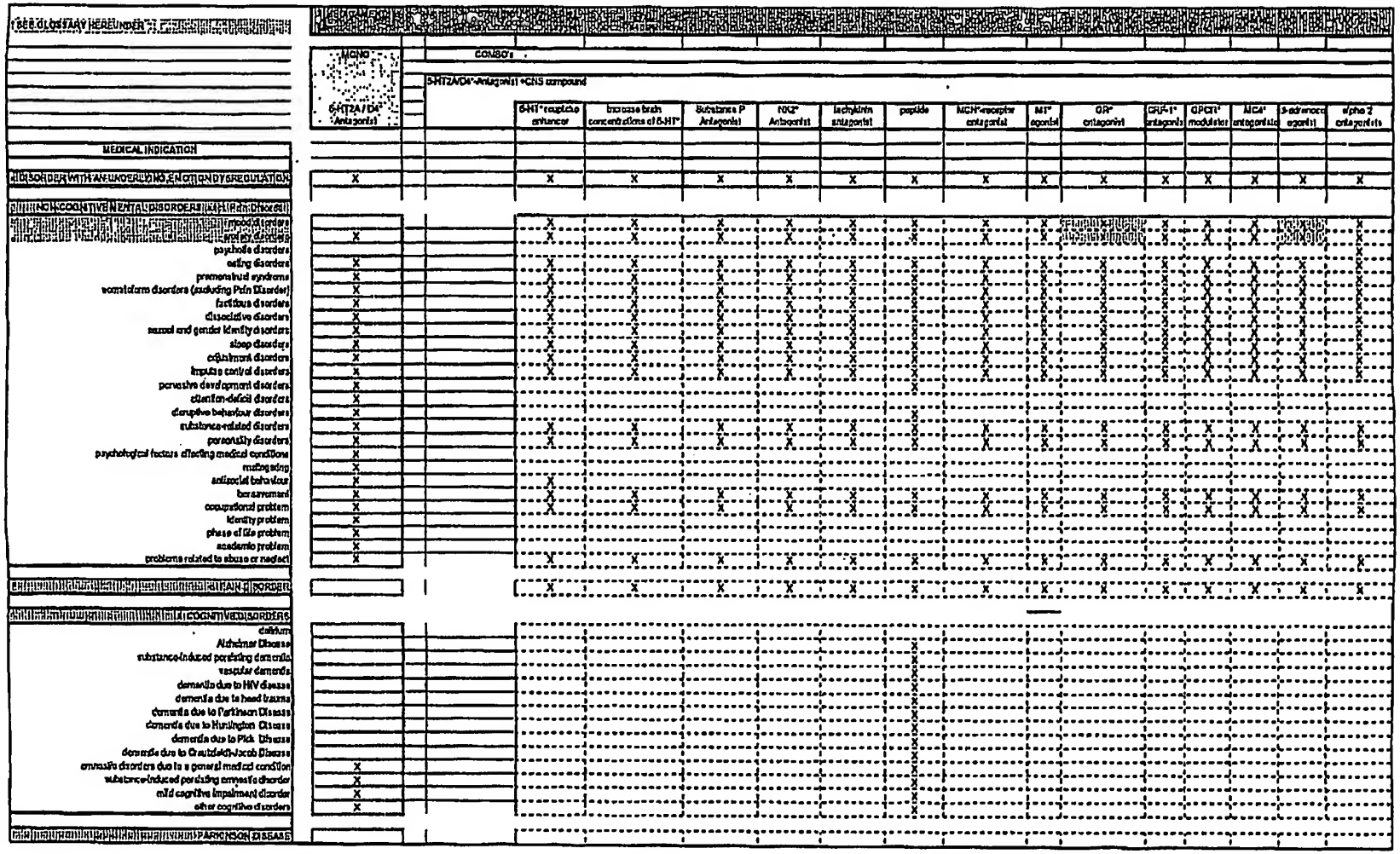
****Q-LES-Q : Quality of Life, Enjoyment and Satisfaction Questionnaire

Table 4

DAY	minus D7	D0	=>D4
TREATMENTGROUP			
Placebo (PLC)	PLC+PLC	2x(PLC+PLC)	2x(PLC+PC)
PIP - Active / Day 4	PLC+PLC	2x(PLC+PIP (4mg))/d	2x(CIT (10mg)+PIP (4mg))/d
PIP - Active / Day 0	PLC+PLC	2x(CIT (10mg)+PIP (4mg))/d	2x(CIT (10mg)+PIP (4mg))/d
PLC - Active / Day 0	PLC+PLC	2x(CIT (10mg)+PLC)/d	2x(CIT (10mg)+PLC)/d

Table 5


MEDICAL INDICATION
MDMD
5-HT2A / D4 Antagonist
COMBOs
5-HT2A/D4 Antagonist + CNS Compound
SSRI
SNRI
SNDRI
SLNRI
NARI
NDRI
NaSSA
RIMA
MAO-A & MAO-B reuptake inhibitor
5-HT1A agonist
5-HT1A antagonist
5-HT1B antagonist
5-HT2B antagonist
5-HT2C antagonist
5-HT3 antagonist
5-HT6 antagonist
5-HT1 autoreceptor agonist
DISORDER WITH AN UNDERLYING EMOTION DYSREGULATION
NON-COGNITIVE MENTAL DISORDERS (excl. PAIN DISORDER)
mood disorders
anxiety disorders
psychotic disorders
eating disorders
premenstrual syndrome
somatoform disorders (excluding Pain Disorder)
factitious disorders
dissociative disorders
sexual and gender identity disorders
sleep disorders
adjustment disorders
impulse control disorders
pervasive development disorders
attention-deficit disorders
disruptive behaviour disorders
substance-related disorders
personality disorders
psychological factors affecting medical conditions
malingering
antisocial behaviour
bereavement
occupational problem
identity problem
phase of life problem
academic problem
problems related to abuse or neglect
PAIN DISORDER
COGNITIVE DISORDERS
delirium
Alzheimer Disease
substance-induced persisting dementia
vascular dementia
dementia due to HIV disease
dementia due to head trauma
dementia due to Parkinson Disease
dementia due to Huntington Disease
dementia due to Pick Disease
dementia due to Creutzfeldt-Jacob Disease
amnestic disorders due to a general medical condition
substance-induced persisting amnestic disorder
mild cognitive impairment disorder
other cognitive disorders
PARKINSON DISEASE



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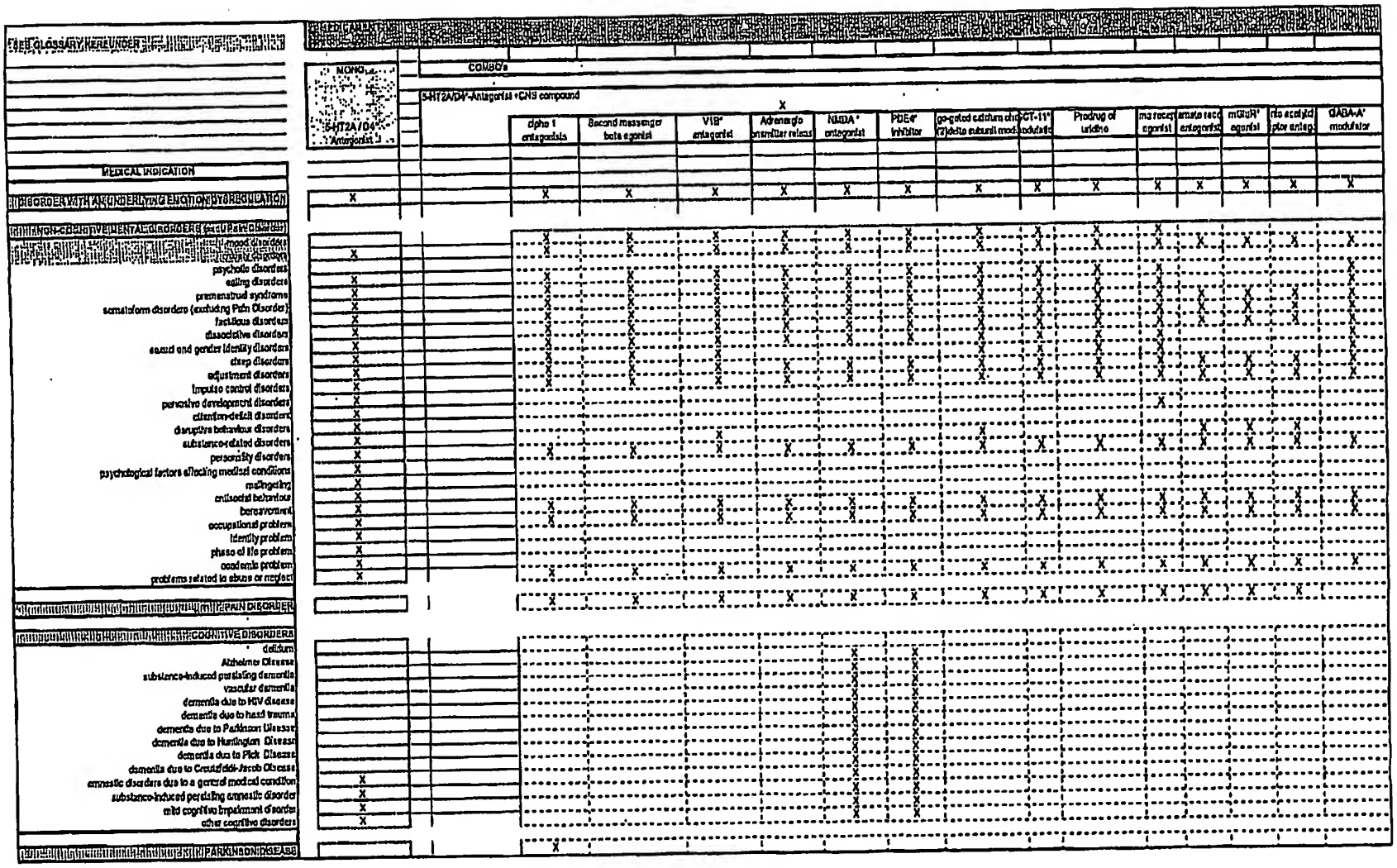

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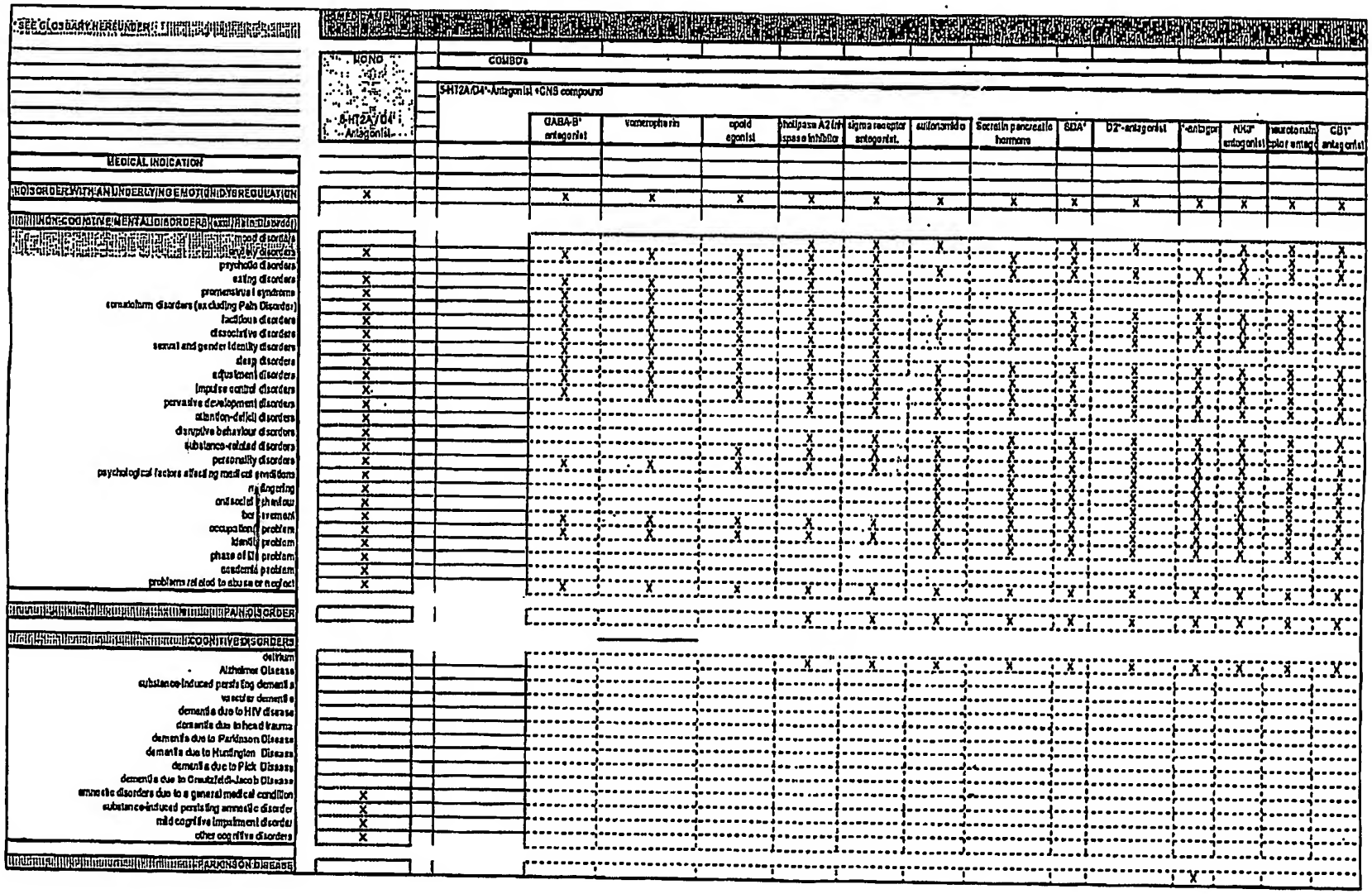
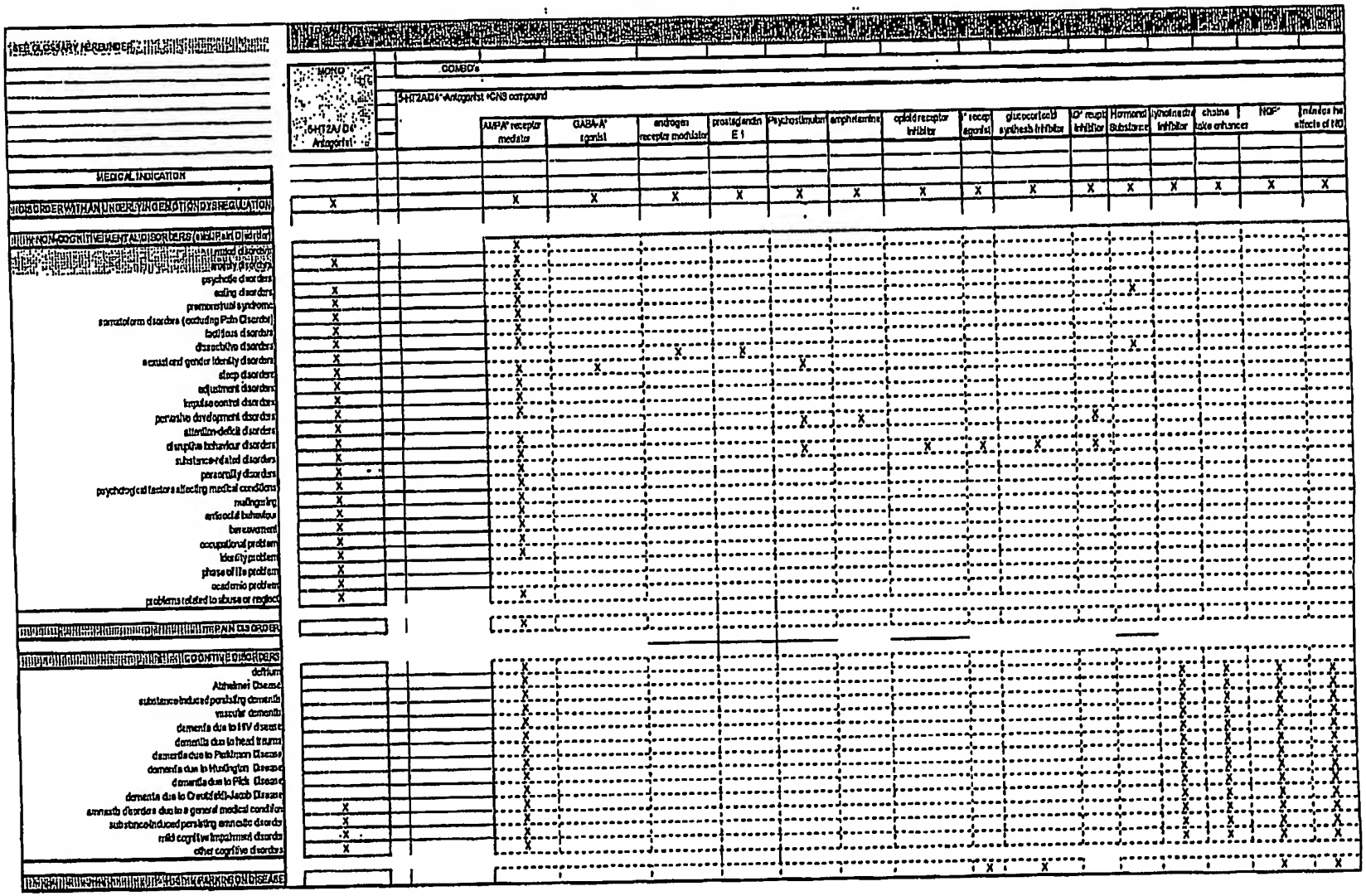


21-10-04;20:40 ;DCB EPO Munchen ;+3292802345 # 0 23



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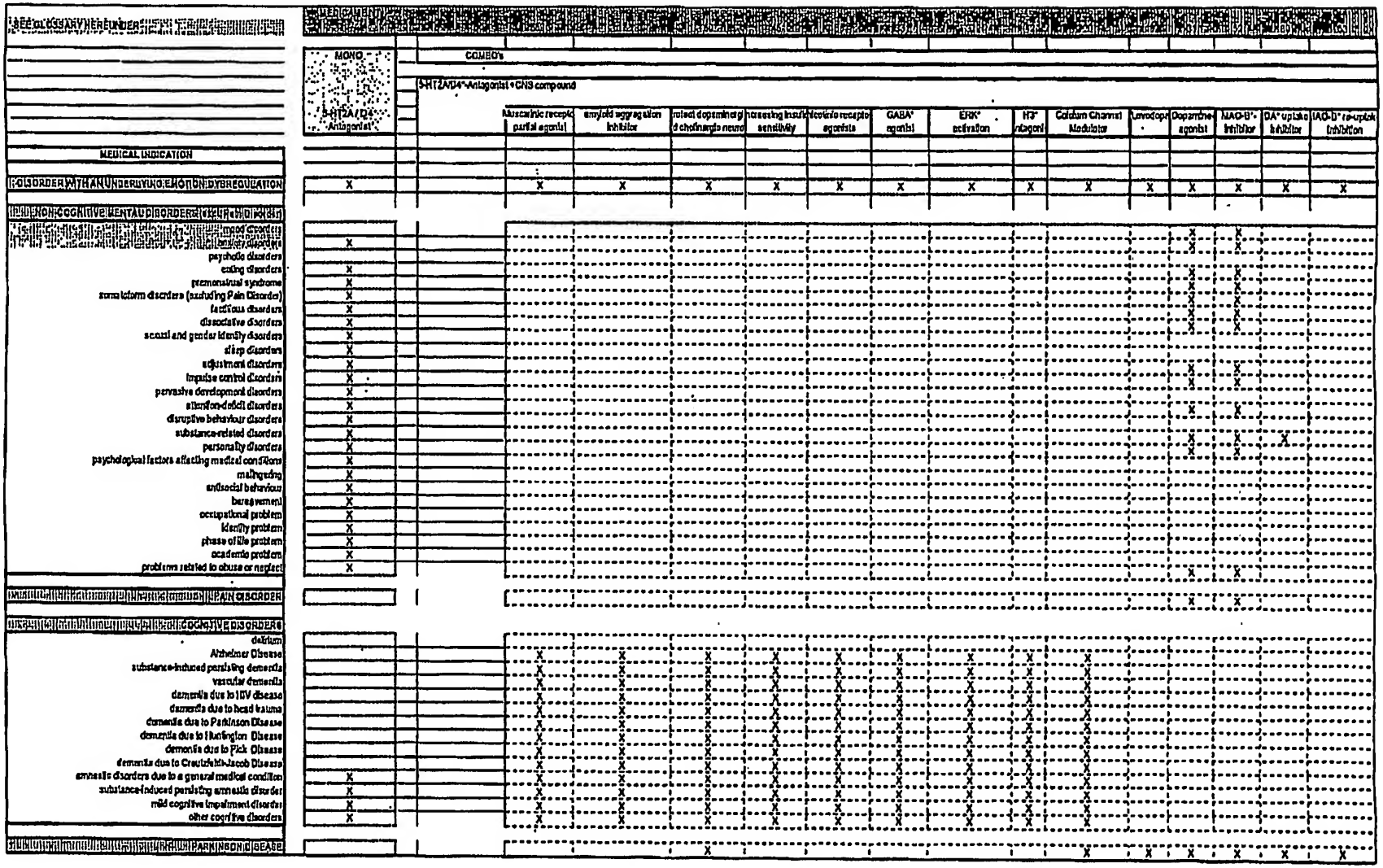

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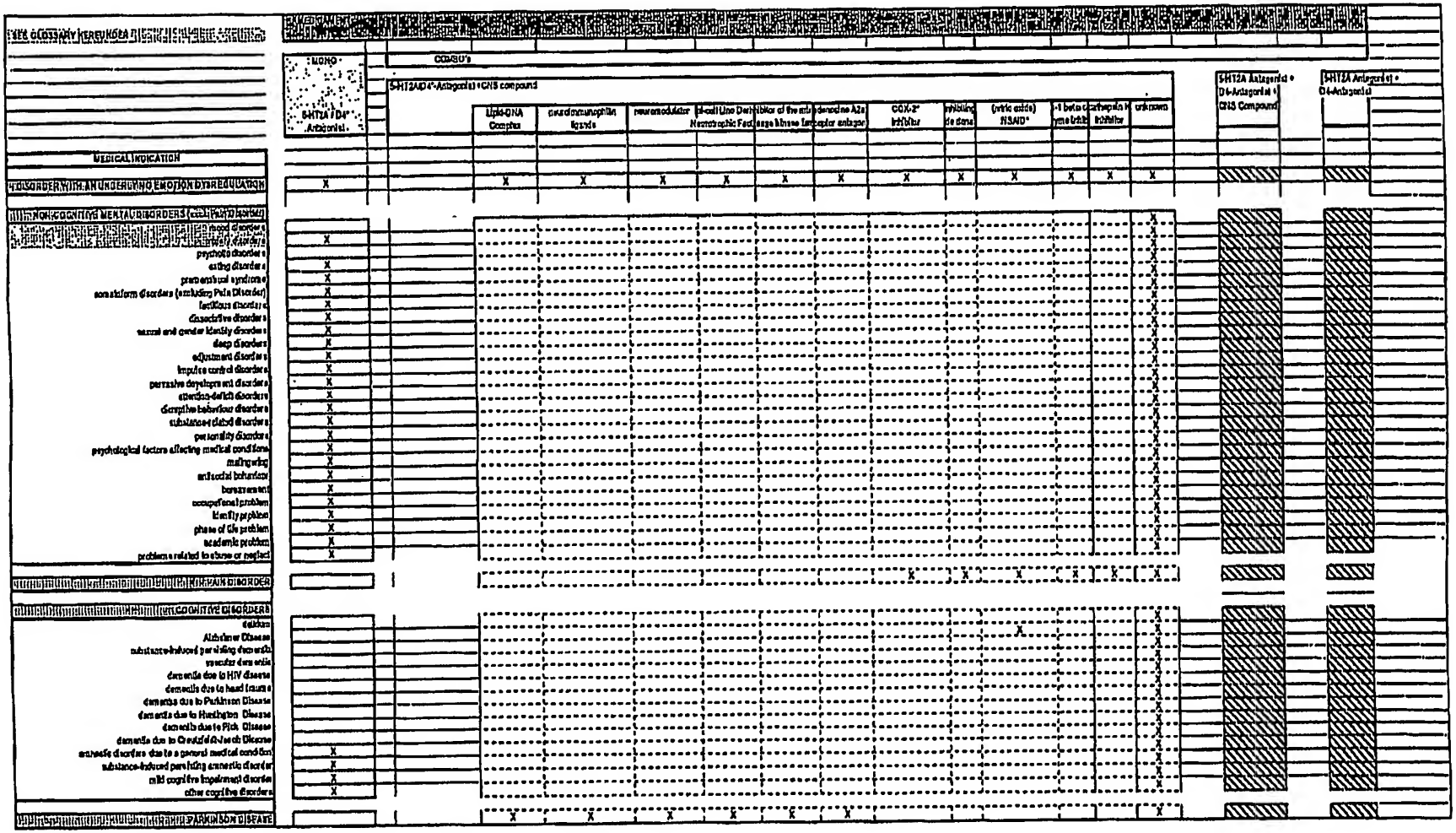

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GLOSSARY
5-HT = serotonin
5-HT1 = serotonin 1 receptor
5-HT1A = serotonin 1A receptor
5-HT1B = serotonin 1B receptor
5-HT2A/D4 = serotonin 2A en dopamine D4 receptor
5-HT2B = serotonin 2B receptor
5-HT2C = serotonin 2C receptor
5HT3 = serotonin 3 receptor
5HT6 = serotonin 6 receptor
AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate
CB1 = cannabioid receptor 1
CINODs = COX-inhibiting nitric oxide donators
COX = cyclooxigenase
COX-2 = cyclooxigenase 2
CRF-1 = Corticotropin-Releasing Factor Receptor 1
D1 = Dopamine 1
D2 = Dopamine 2
D2 = Dopamine 3
DA = Dopamine
ERK = extracellular signal-related kinase
GABA = gamma-aminobutyric acid
GABA-A = gamma-aminobutyric acid A receptor
GABA-B = gamma-aminobutyric acid B receptor
GPCR = G-Protein-Coupled Receptor
GR = glucocorticoid receptor
H3 = histamine H3-receptor
MAO = mono-amine oxydase
MAO-A = mono-amine oxydase A
MAO-B = mono-amine oxydase B
MC4 = melanocortin-4 receptor
MCH = Melanin concentrating hormone
MgluR = metabotropic glutamate receptor
MT = melatonin receptor
NARI = selective nor-adrenaline re-uptake inhibitor
NaSSA = noradrenergic/specific serotonergic antidepressant
NDRI = selective nor-adrenaline and dopamine re-uptake inhibitor
NGF = Nerve Growth Factor
NGF = nerve growth factor
NK1 = neurokinin 1 receptor
NK2 = neurokinin 2 receptor
NK3 = neurokinin 3 receptor
NMDA = N-Methyl-D-aspartate
NSAID = Non-steroidal anti-inflammatory drugs
PDE4 = phosphodiesterase-4
RIMA = reversible inhibitor of mono-amine oxydase A
SCT-11 = G protein-coupled receptor
SDA = Serotonin/Dopamine Antagonist
SDRI = selective serotonin and dopamine reuptake inhibitor
SNDRI = selective serotonin, nor-adrenaline and dopamine reuptake inh
SNRI = selective serotonin and nor-adrenaline reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor
V1B = vasopressin 1B receptor

21-10-04;20:40 ;DCB EPO Munchen ;+3292802545 # D- 27

Table 6

PHARMAC. GROUP (see overview hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Monoaminergic Transmitter Systems	1	5-HT reuptake enhancer	Depression / Anxiety	Tianeptine	25 to 50mg daily	Servier
Monoaminergic Transmitter Systems	2	5-HT1 autoreceptor agonist	Depression / Anxiety	SUNEPITRON	unknown	Pfizer
Monoaminergic Transmitter Systems	3	5HT1A agonist	Anxiety	MN-305		MediciNova
		5-HT1A agonist	Depression / Anxiety	Buspirone		Bristol-Myers Squibb
		5-HT1A agonist	Depression	bupropion (controlled release formulation / once-day)	150mg to 450mg	GlaxoSmithKline
		5-HT1A agonist	Depression	gepirone	20mg to 60mg daily	Organon
		5-HT1A agonist	Alzheimer's Disease	Xaliproden	1 to 2mg daily	Sanofi-Synthelabo
		5-HT1A agonist	Depression / Anxiety	Flesinoxan	unknown	Solvay
		5-HT1A agonist	Anxiety	Isapiron		Esteve
		5-HT1A agonist	Depression	VPI-013 (also known as OPC-14523)		Vela, Otsuka
		5-HT1A agonist	Depression / Anxiety	metanospirone		?
		5-HT1A agonist	Depression / Anxiety	EMD 68843		EMD Pharmaceuticals
		5-HT1A agonist	Depression / Anxiety	alnespirone		Servier
		5-HT1A agonist	Depression / Anxiety	tandospirone		Sumitomo
		5-HT1A agonist	Depression / Anxiety	zalospirone		Wyeth
		5-HT1A agonist	Parkinson's Disease	sarizotan	unknown	EMD Pharmaceuticals
		5-HT1A agonist	ADHD	PRX-00023		Predix
		5-HT1A agonist	Anxiety	PRX-00023		Predix
Monoaminergic Transmitter Systems	4	5-HT1A antagonist	Depression	robalzotan tartrate hydrate	unknown	AstraZeneca
		5-HT1A antagonist	Depression	NAD299		AstraZeneca
Monoaminergic Transmitter Systems	5	5-HT1B antagonist	Depression / Anxiety	AR-A2		AstraZeneca
		5-HT1B antagonist	Depression / Anxiety	elzasonan	unknown	Pfizer
		5-HT1B antagonist	Depression / Anxiety	AZD1134		AstraZeneca
Monoaminergic Transmitter Systems	6	5-HT2B antagonist	Depression / Anxiety	Agomelatine	25 to 50mg daily	Servier
Monoaminergic Transmitter Systems	7	5-HT2C antagonist	Depression / Anxiety	Agomelatine	25 to 60mg daily	Servier
		5-HT2C antagonist	Depression / Anxiety	SB 243213		GlaxoSmithKline
Monoaminergic Transmitter Systems	8	5-HT3 antagonist	Cocaine Dependence	ondansetron	8 to 32mg daily	National Institute on Drug Abuse
Monoaminergic Transmitter Systems	9	5-HT6 antagonist	Alzheimer's Disease	SB-271046		GlaxoSmithKline
		5-HT6 antagonist	Alzheimer's Disease	271046		GlaxoSmithKline
		5-HT6 antagonist	Alzheimer's Disease	742457		GlaxoSmithKline
Excitatory Amino Acid System	10	acetylcholinesterase inhibitor	Alzheimer's Disease	dichlorvos		Bayer
		acetylcholinesterase inhibitor	Alzheimer's Disease	metrifonate		Bayer
		acetylcholinesterase inhibitor	Alzheimer's Disease	physostigmine		Lundbeck / Forest Laboratories
		acetylcholinesterase inhibitor	Alzheimer's Disease	rivastigmine		Novartis Pharmaceuticals
		acetylcholinesterase inhibitor	Alzheimer's Disease	tacrine		Parke Davis
		acetylcholinesterase inhibitor	Alzheimer's Disease	donepezil		Pfizer
		acetylcholinesterase inhibitor	Alzheimer's Disease	galantamine (extended release formulation)	8 to 24mg daily	Johnson & Johnson Pharmaceutical
		acetylcholinesterase inhibitor	Alzheimer's Disease	phenserine tartrate	20 to 30mg daily	Axonyx
		acetylcholinesterase inhibitor	Alzheimer's Disease	huperzine A		Interneuron
		acetylcholinesterase inhibitor	Alzheimer's Disease	rivastigmine butyrate	1 to 2mg daily	Novartis Pharmaceuticals
		acetylcholinesterase inhibitor	Alzheimer's Disease	ensaculin hydrochloride		Schwabe
Adenosine Transmitter System	11	adenosine A2a receptor antagonist	Parkinson's Disease	KW-6002	40 to 80mg daily	Kyowa Pharmaceutical
Monoaminergic Transmitter Systems	12	Adrenergic transmitter releaser	Depression	[illegible]	30 to 60mg daily	Sanofi
Monoaminergic Transmitter Systems	13	alpha 1 adrenoreceptor antagonist	Depression / Anxiety	Flesinoxan	unknown	Solvay
		alpha 1 adrenoreceptor antagonist	Parkinson's Disease	SDZ NVI 085	unknown	Sandoz
Monoaminergic Transmitter Systems	14	alpha 2 adrenoreceptor antagonist.	Depression	Mirtazapine		Organon
		alpha 2 adrenoreceptor antagonist.	Depression	idazoxan	20mg daily	Reckitt and Colman
		alpha 2 adrenoreceptor antagonist.	Schizophrenia	idazoxan	20mg daily	Reckitt and Colman
		alpha 2 adrenoreceptor antagonist.	Depression / Anxiety	SUNEPITRON	unknown	Pfizer
		alpha 2 adrenoreceptor antagonist.	Depression	fluparoxan		GlaxoSmithKline
		alpha 2 adrenoreceptor antagonist.	Depression / Anxiety	(R)-A 75200		Abbott
		alpha 2 adrenoreceptor antagonist.	Depression / Anxiety	A 75200		Abbott
		alpha 2 adrenoreceptor antagonist.	Insomnia	Mirtazapine		Organon
		alpha 2 adrenoreceptor antagonist.	Depression	UK-14304		?
Excitatory Amino Acid System	15	AMPA receptor mediator	Alzheimer's Disease	ampakine CX-516		Cortex Pharmaceuticals / Organon
		AMPA receptor mediator	Alzheimer's Disease	ampakine CX-717	unknown	Cortex Pharmaceuticals / Organon
		AMPA receptor mediator	Schizophrenia	ampakine ORG 24448/CX-619	unknown	Organon
		AMPA receptor mediator	Depression	Ampakine CX-691	unknown	Cortex Pharmaceuticals / Organon

PHARMAC. GROUP (see overview hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Excitatory Amino Acid System	16	amphetamine	ADHD	methylphenidate transdermal system		Noven Pharmaceuticals
Pathogenic Mechanisms of Dementia of the Alzheimer Type	17	amyloid aggregation-inhibitor	Alzheimer's Disease	Alzhemed	200 to 300mg daily	Neurochem
		amyloid aggregation-inhibitor	Alzheimer's Disease	APAN		Praecis Pharmaceutical
Endocrine System	18	androgen receptor modulator	Female Sexual Dysfunction	LGD2226		Ligand Pharmaceuticals
Monoaminergic Transmitter Systems	19	beta 3 adrenoreceptor agonist	Depression / Anxiety	SR 58611	unknown	Sanofi-Synthelabo
Other / Unknown	20	Calcium Channel Modulator	Alzheimer's Disease	MEM 1003		Memory Pharmaceuticals
		Calcium Channel Modulator	Parkinson's Disease	safinamide		Newron Pharmaceuticals
Monoaminergic Transmitter Systems	21	cannabinoid receptor antagonist	Schizophrenia	SR 141716	unknown	Sanofi-Synthelabo
Enzymatic System	22	cathepsin K inhibitor	Pain	462795		GlaxoSmithKline
Excitatory Amino Acid System	23	choline uptake enhancer	Alzheimer's Disease	MKC-231	20 to 160mg daily	Mitsubishi Pharma
Enzymatic System	24	COX-2 inhibitor	Pain	celecoxib		Pfizer
		COX-2 inhibitor	Pain	rofecoxib		Pfizer
		COX-2 inhibitor	Pain	valdecoxib		Pfizer
		COX-2 inhibitor	Pain	etoricoxib	20 to 120mg daily	Merck
		COX-2 inhibitor	Pain	COX 189	100 to 800mg daily	Novartis Pharmaceuticals
		COX-2 inhibitor	Pain	parecoxib	20 to 80mg daily	Pfizer
		COX-2 inhibitor	Pain	ABT-963		Abbott
Enzymatic System	25	COX-inhibiting nitric oxide donators (CINODs)	Pain	AZD3582	375mg daily	AstraZeneca
		COX-inhibiting nitric oxide donators (CINODs)	Pain	AZD4717		AstraZeneca
Endocrine System	26	CRF1 antagonist	Depression	AAG561	unknown	Novartis Pharmaceuticals
		CRF1 antagonist	Depression / Anxiety	R121919	5 to 80mg daily	Johnson & Johnson Pharmaceutical
		CRF1 antagonist	Depression / Anxiety	idzosan	unknown	Pfizer
		CRF1 antagonist	Depression	723620		GlaxoSmithKline
		CRF1 antagonist	Depression / Anxiety	NBI-34041		Neurocrine Biosciences
		CRF1 antagonist	Depression / Anxiety	CP-154-526		Pfizer
		CRF1 antagonist	Depression / Anxiety	CP-448,187		Pfizer
Monoaminergic Transmitter Systems	27	D1 receptor agonist	Cocaine Dependence	DAS-431	unknown	Drug Abuse Sciences
Monoaminergic Transmitter Systems	28	D2 receptor antagonist	Schizophrenia	amisulpride		off patent
		D2 receptor antagonist	Schizophrenia	bifeprunox	unknown	Solvay
Monoaminergic Transmitter Systems	29	D3 antagonist	Cocaine Dependence	BSF-201640		?
		D3 antagonist	Cocaine Dependence	PD 58491		?
		D3 antagonist	Parkinson's Disease	BSF-201640		?
		D3 antagonist	Parkinson's Disease	PD 58491		?
		D3 antagonist	schizophrenia	BSF-201640		?
		D3 antagonist	schizophrenia	PD 58491		?
Monoaminergic Transmitter Systems	30	DA uptake inhibitor	Cocaine Dependence	GBR 12909		National Institute on Drug Abuse
		DA uptake inhibitor	Parkinson's Disease	safinamide		Newron Pharmaceuticals
Monoaminergic Transmitter Systems	31	dopamine agonist	Parkinson's Disease	sumanirole	4 to 16mg daily	Pfizer
		dopamine agonist	Parkinson's Disease, Early and Advanced	rotigotine CDS (Once-a-Day Transdermal Patch)	4.5 to 13.5mg daily	Schwarz Pharma
		dopamine agonist	Parkinson's Disease Restless Leg	ropinirole HCL (controlled-release formulation)	0.75 to 24mg daily	GlaxoSmithKline
		dopamine agonist	Cocaine Dependence	cabergoline		Abbott
		dopamine agonist	Parkinson's Disease	sarizotan		EMD Pharmaceuticals
		dopamine agonist	Parkinson's Disease	pramipexole		Pfizer
		dopamine agonist	Parkinson's Disease	DAB452		Wyeth
		dopamine agonist	Parkinson's Disease, Comorbid	SLV 308		Solvay
		dopamine agonist	Depression / Anxiety	S32504		Servier
		dopamine agonist	Parkinson's Disease	S32504		Servier
		dopamine agonist	Parkinson's Disease	bromocriptine		Novartis Pharmaceuticals
		dopamine agonist	Parkinson's Disease	alap5de		VU-Res. Inst. Pharm. Biochem (CZ)

PHARMAC. GROUP (see overview hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Enzymatic System	32	ERK activation	Alzheimer's Disease	CPI-1189	50 to 100mg daily	Centaur Pharmaceuticals
Inhibitory Amino Acid System	33	GABA agonist	Alzheimer's Disease	Nefiracetam	unknown	Daiichi Seiyaku, JPN Nattermann, BRD
Inhibitory Amino Acid System	34	GABA-A agonist	Insomnia	Gaboxadol	5 to 20mg daily	Lundbeck
Inhibitory Amino Acid System	35	GABA-A modulator	Insomnia	eszopiclone	2 to 3mg daily	Sepracor
		GABA-A modulator	Insomnia	Zolpidem MR sustained-release version	10 to 20mg daily	Sanofi-Synthelabo
		GABA-A modulator	Insomnia	indiplon	10 to 20mg daily	DOV / Neurocrine
		GABA-A modulator	Anxiety	Pagoclone	30mg daily	Indevus
		GABA-A modulator	Insomnia	Zaleplon extended-release	10mg daily	King Pharmaceuticals
		GABA-A modulator	Anxiety	SEP174559		Sepracor
		GABA-A modulator	Anxiety, muscular contractions	SL 65.1498		Sanofi-Synthelabo
		GABA-A modulator	Insomnia	CP-730,330 (NGD 96-3)		Neurogen
		GABA-A modulator	Insomnia	NGD 96-3		Neurogen
		GABA-A modulator	Anxiety	Ocinaplon	10 to 60mg daily	DOV
Inhibitory Amino Acid System	36	GABA-B antagonist	Depression / Anxiety	AVE [illegible]	unknown	Aventis
Neurotrophic System	37	Glial-cell Line Derived Neurotrophic Factor	Parkinson's Disease	GDNF	15mg daily	Amgen
Endocrine System	38	glucocorticoid synthesis inhibitor	Cocaine Dependence	metyrapone		National Institute on Drug Abuse
Excitatory Amino Acid System	39	Glutamate receptor antagonist	Anxiety	LY354740		Eli Lilly
Other / Unknown	40	GPCR modulator	Depression / Anxiety	R1204		Roche
Endocrine System	41	GR antagonist	depression (psychotic)	Mifepristone	600 to 1200mg daily	Corcept
		GR antagonist	Depression	ORG 34517/34850	unknown	Organon
Monoaminergic Transmitter Systems	42	H3 Antagonist	Alzheimer's Disease	ABT-239		Abbott
		H3 Antagonist	Alzheimer's Disease	ABT-834		Abbott
Endocrine System	43	Hormonal Substance	Premenstrual Syndrome	drospirenone 3mg/ethinyl estradiol 0.020mg daily	see formula	Berlex Laboratories
		Hormonal Substance	Female Sexual Dysfunction	female testosterone patch		Procter & Gamble Pharmaceuticals
		Hormonal Substance	Premenstrual Syndrome	synthetic conjugated estrogen A	0.3mg daily	Barr Laboratories
		Hormonal Substance	Female Sexual Dysfunction	testosterone gel		BioSante Pharmaceuticals
		Hormonal Substance	Female Sexual Dysfunction	testosterone gel		Cellegy Pharmaceuticals
		Hormonal Substance	Female Sexual Dysfunction	methyltestosterone		Noven Pharmaceuticals
		Hormonal Substance	Female Sexual Dysfunction	estrogens/methyltestosterone		Solvay
		Hormonal Substance	Female Sexual Dysfunction	testosterone transdermal spray		VIVUS
Monoaminergic Transmitter Systems	44	Increase brain concentrations of 5-HT	Depression / Anxiety	KW 6055		?
		Increase brain concentrations of 5-HT	Depression / Anxiety	PMD 145		?
		Increase brain concentrations of 5-HT	Depression / Anxiety	SP 188		?
		Increase brain concentrations of 5-HT	Depression / Anxiety	Triplosine		?
Endocrine System	45	Increasing insulin sensitivity	Alzheimer's Disease	rosiglitazone maleate		GlaxoSmithKline
Enzymatic System	46	Inhibitor of the mixed lineage kinase family	Parkinson's Disease	CEP-1347	unknown	Cephalon
Enzymatic System	47	Interleukin-1 beta converting enzyme inhibitor	Pain	pralnacasan		Aventis
Monoaminergic Transmitter Systems	48	levodopa	Parkinson's Disease	etilevodopa	unknown	TEVA Pharmaceuticals USA
Other / Unknown	49	Lipid-DNA Complex	Parkinson's Disease	GR213487B		Valentis
Monoaminergic Transmitter Systems	50	MAO reuptake inhibitor	Cocaine Dependence	NS 2359		National Institute on Drug Abuse
Monoaminergic Transmitter Systems		MAO reuptake inhibitor	ADHD	NS 2359		NeuroSearch
Monoaminergic Transmitter Systems	51	MAO-A & MAO-B reuptake inhibitor	ADHD	SPD473	unknown	Shire Pharmaceutical Development
Monoaminergic Transmitter Systems	52	MAO-B inhibitor	Depression	EmSam (transdermal selegiline)		Somerset
		MAO-B inhibitor	Parkinson's Disease	selegiline	5 to 10mg daily	Amarin Pharmaceuticals
		MAO-B inhibitor	Parkinson's Disease	rasagiline (TVP-1012)	1 to 2mg daily	TEVA Pharmaceuticals USA / Lundbeck
Monoaminergic Transmitter Systems	53	MAO-B re-uptake inhibition	Parkinson's Disease	safinamide		Newron Pharmaceuticals
Peptidergic Transmitter System	54	MC4 antagonists	Depression / Anxiety	MCL0129		Taisho
Peptidergic Transmitter System	55	MCH receptor antagonist	Depression	SNAP-7941		Synaptic
Endocrine System	56	melatonin receptor agonist	Insomnia	Ramelteon	unknown	Takeda
		melatonin receptor agonist	Depression / Anxiety	Agomelatine	25 to 50mg daily	Servier
Excitatory Amino Acid System	57	MgluR agonist	Anxiety	PRE703		Prescient
Neurotrophic System	58	mimics the effects of NGF	Alzheimer's Disease	Xaliproden	1 to 2mg daily	Sanofi-Synthelabo
Excitatory Amino Acid System	59	Muscarinic receptor partial agonist	Alzheimer (JP) / Sjogren (US)	Cevimeline	unknown	Daiichi Seiyaku
Monoaminergic Transmitter Systems	60	NARI	Depression / Anxiety	reboxetine		Pfizer
		NARI	ADHD	atomoxetine hydrochloride	40 to 100mg daily	Eli Lilly
		NARI	Depression	reboxetine	8 to 12mg daily	Pfizer
		NARI	ADHD	165U88		GlaxoSmithKline
		NARI	Depression / Anxiety	(S)-A 76200		Abbott
		NARI	Depression / Anxiety	A 76200		Abbott

PHARMAC. GROUP (see overview hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Monoaminergic Transmitter Systems	61	NaSSA	Insomnia	ORG 4420	unknown	Organon
Monoaminergic Transmitter Systems	62	NDRI	Depression (bipolar disorder)	GW353162	20 to 60mg daily	GlaxoSmithKline
Neuroimmunophilin System	63	neuroimmunophilin ligands	Parkinson's Disease	GPI 1485	200 to 1000mg daily	Guilford Pharmaceuticals
Adenosine Transmitter System	64	neuromodulator	Parkinson's Disease	adenosine		Schering-Plough
Peptidergic Transmitter System	65	neurotensin receptor antagonist	Schizophrenia	SR 48692	10 to 200mg daily	Sanofi-Synthelabo
Neurotrophic System	66	NGF (nerve growth factor)	Alzheimer's Disease	nerve growth factor (NGF) gene therapy		Ceregene
Excitatory Amino Acid System	67	nicotinic acetylcholine receptor antagonist	Anxiety	SEP174559	unknown	Sepracor
Excitatory Amino Acid System	68	nicotinic receptor agonists	Alzheimer's Disease	ABT-089	4 to 20mg daily	Abbott
Peptidergic Transmitter System	69	NK2 antagonist	Depression / Anxiety	saredutant	100mg daily	Sanofi-Synthelabo
Peptidergic Transmitter System	70	NK3 antagonist	Schizophrenia	osanetant		Sanofi-Synthelabo
		NK3 antagonist	Schizophrenia / IBS / Over active bladder	talnetant	[illegible]mg daily	GlaxoSmithKline
Excitatory Amino Acid System	71	NMDA antagonist	Anxiety	SEP174559		Sepracor
		NMDA antagonist	Alzheimer's Disease	memantine	20mg daily	Lundbeck / Forest Laboratories
		NMDA antagonist	Depression	memantine	20mg daily	Lundbeck / Forest Laboratories
		NMDA antagonist	Pain	memantine	40mg daily	Lundbeck / Forest Laboratories
		NMDA antagonist	Depression	Delucemine		NPS
Enzymatic System	72	NSAID	Pain	meloxicam		Boehringer-Ingelheim Pharmaceuticals
		NSAID	Pain	piroxicam		off patent
		NSAID	Alzheimer's Disease	Flurizan (pure R-enantiomer form of flurbiprofen)	unknown	Myriad Genetics
		NSAID	Pain	LAX-1094		Medinox
Excitatory Amino Acid System	73	opioid antagonist	Alcohol/Drug Dependence	naltrexone depot	[illegible] to 384mg	Drug Abuse Sciences
		opioid antagonist	Opiate/Alcohol Dependence	depot naltrexone microcapsules		Biotek
Excitatory Amino Acid System	74	opioid agonist	Anxiety	[illegible]	unknown	Lundbeck / Forest
		opioid agonist	Cocaine Dependence	cyclazocine		National Institute on Drug Abuse
		opioid agonist	Schizophrenia	E-6842		Esteve
Enzymatic System	75	PDE4 inhibitor	Depression	ND1251		Neuro3d
		PDE4 inhibitor	Alzheimer's disease	MEM 1917 (R1497)		Roche / Memory Pharm
		PDE4 inhibitor	Depression	MEM 1917 (R1497)		Roche / Memory Pharm
Peptidergic Transmitter System	76	peptide	Depression	INN 00835	8 (0.16mg daily)	Innapharma
		peptide	Autism	secretin	0.2 to 0.4mg/kg daily	Repligen
		peptide	Female Sexual Dysfunction	PT-141		Palatin Technologies
		peptide	Alzheimer's Disease	beta-sheet breaker peptide		Serono
Enzymatic System	77	Phospholipase A 2 inhibitor with caspase inhibitor activity	Depression	LAX-101c	unknown	Laxdale
		Phospholipase A 2 inhibitor with caspase inhibitor activity	Depression (bipolar disorder)	LAX-101b		Laxdale
		Phospholipase A 2 inhibitor with caspase inhibitor activity	Schizophrenia	LAX-101a		Laxdale
Nucleosides	78	Prodrug of uridine	depression (bipolar disorder)	RG2133 (triacetyluridine)	unknown	Repligen
Endocrine System	79	prostaglandin E 1	Female Sexual Dysfunction	alprostadil gel	50 to 300 microgram/application	VIVUS
		Prostaglandin E1	Female Sexual Dysfunction	alprostadil cream		NexMed
Neurotrophic System	80	protect dopaminergic and cholinergic neurons	Alzheimer's Disease	SR 57667	unknown	Sanofi-Synthelabo
Excitatory Amino Acid System	81	Psychostimulant	ADHD	modafinil	200 to 600mg daily	Cephalon
		Psychostimulant	ADHD	SPD 603	unknown	Shire Pharmaceutical Development
		Psychostimulant	Hypersomnia	r-modafinil		Cephalon
		Psychostimulant	Cocaine Dependence	modafinil		National Institute on Drug Abuse
Monoaminergic Transmitter Systems	82	RIMA	Depression / Anxiety	moclobemide		Roche
		RIMA	Depression / Anxiety	toloxatone		Sanofi-Synthelabo
		RIMA	Depression / Anxiety	befloxatone	[illegible]mg daily	Sanofi-Synthelabo
		RIMA	Depression	caroxazone F.16654		Farmitalia
		RIMA	Depression / Anxiety	cimoxatone		MD
		RIMA	Depression / Anxiety	RS 8359		Sankyo

PHARMAC. GROUP (see overview hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Other / Unknown	83	SCT-11 modulation	Depression	SNEC-2		Synaptic
Monoaminergic Transmitter Systems	84	SDA	Schizophrenia	quetiapine		AstraZeneca
		SDA	Schizophrenia	aripiprazole		Bristol-Myers Squibb
		SDA	Schizophrenia	risperidone		Johnson & Johnson Pharmaceutical
		SDA	Schizophrenia	zolepine		Knoll / BASF
		SDA	Schizophrenia	olanzapine		Lilly
		SDA	Schizophrenia	clozapine		Novartis Pharmaceuticals
		SDA	Schizophrenia	ziprasidone		Pfizer
		SDA	Depression (Bipolar Maintenance)	olanzapine		Eli Lilly
		SDA	Schizophrenia	perospirone	unknown	Sumitomo
		SDA	Schizophrenia	blonanserin	unknown	Almirall Prodesfarma
		SDA	Alzheimer's Disease	olanzapine		Eli Lilly
		SDA	Alzheimer's Disease	aripiprazole		Bristol-Myers Squibb
		SDA	Schizophrenia	quetiapine fumarate (granules)		AstraZeneca
		SDA	Schizophrenia	quetiapine fumarate (sustained release)		AstraZeneca
		SDA	Schizophrenia	paliperidone	6 to 12 mg daily	Johnson & Johnson Pharmaceutical
		SDA	Schizophrenia	asenlindole	12 to 24mg daily	Lundbeck
		SDA	Schizophrenia	lloperidone		Novartis Pharmaceuticals
		SDA	Schizophrenia	bifeprunox	10mg daily	Organon
		SDA	Schizophrenia	SLV-311-0177	unknown	Sanofi-Synthelabo
		SDA	Schizophrenia	lu 31-130	unknown	Solvay
		SDA	Schizophrenia	ocaperidone		Neurogen
		SDA	Schizophrenia	SM-13496		Sumitomo
		SDA	Schizophrenia	LU 31-131		Lundbeck
		SDA	Schizophrenia	BSF-190555		?
		SDA	Schizophrenia	S-18327		Servier
Monoaminergic Transmitter Systems	85	SDRI	Depression / Anxiety	Bazinaprine		Sanofi-Synthelabo
Monoaminergic Transmitter Systems	86	Second messenger beta agonist	Depression	ropinirol	1.5 to 3mg daily	Shering
		Second messenger beta agonist	Depression	SR 57227		Sanofi-Synthelabo
		Second messenger beta agonist	Depression	eplivanserin		Sanofi-Synthelabo
		Second messenger beta agonist	Insomnia	eplivanserin		Sanofi-Synthelabo
Endocrine System	87	Secretin pancreatic hormone	Anxiety	RG1068	unknown	Repligen
		Secretin pancreatic hormone	Schizophrenia	RG1068	unknown	Repligen
Excitatory Amino Acid System	88	sigma receptor agonist	Depression	YFI-013 (also known as OPC 14523)	unknown	Vela, Otsuka
		sigma receptor agonist	ADHD	PRX-00023		Predix
		sigma receptor agonist	Anxiety	PRX-00023		Predix
Excitatory Amino Acid System	89	sigma receptor antagonist	Depression / Anxiety	EMD 57445	50mg daily	EMD Pharmaceuticals
		Sigma receptor antagonist	Schizophrenia	SR 31742	unknown	Sanofi-Synthelabo
Monoaminergic Transmitter Systems	90	SNDRI	Alzheimer's Disease	NS 2330	unknown	Boehringer-Ingelheim Pharmaceuticals
		SNDRI	Depression / Anxiety	DOV 216,303	unknown	DOV
		SNDRI	Alzheimer's disease	DOV 21,947		DOV
		SNDRI	Depression	DOV 21,947		DOV
		SNDRI	Depression	McN 5652		McNeil
Monoaminergic Transmitter Systems	91	SNRI	Depression	milnacipran	50 to 200mg daily	Pierre Fabre
		SNRI	Depression / Anxiety	nefazodone		Mead Johnson
		SNRI	Depression / Anxiety	amoxapine		Wyeth
		SNRI	Depression / Anxiety	venlafaxine	75 to 300mg daily	Wyeth
		SNRI	Depression / Anxiety	duloxetine	20 to 60mg daily	Eli Lilly
		SNRI	ADHD	atomoxetine	1.0mg/kg/day	Lilly
		SNRI	Depression / Anxiety	desvenlafaxine	unknown	Wyeth
		SNRI	Depression	talopram		Lundbeck
		SNRI	Depression	talopram		Lundbeck / Wyeth
		SNRI	Depression	tandamine		Wyeth
		SNRI	Depression	LY 113,621		Lilly

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PHARMAC. GROUP (see overview hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Monoaminergic Transmitter Systems	92	SSRI	Depression / Anxiety	paroxetine		GlaxoSmithKline
		SSRI	Depression / Anxiety	escitalopram	10 to 20mg daily	Lundbeck / Forest Laboratories
		SSRI	Depression / Anxiety	citalopram	10 to 40 mg daily	off patent
		SSRI	Depression / Anxiety	fluoxetine		off patent
		SSRI	Depression / Anxiety	fluvoxamine		off patent
		SSRI	Depression / Anxiety	sertraline		Pfizer
		SSRI	Anxiety (OCD / Soc Phobia)	fluvoxamine controlled release	100 to 300mg daily	Solvay
		SSRI	Depression / Anxiety	[illegible]	unknown	Sanofi-Synthelabo
		SSRI	Depression / Anxiety	femoxetine		Ferrosan
		SSRI	Depression / Anxiety	ifoxetine		Novartis Pharmaceuticals
		SSRI	Depression	VPI-013 (also known as OPC-14523)		Vela, Otsuka
		SSRI	Depression / Anxiety	EMD 68843		EMD Pharmaceuticals
		SSRI	Depression / Anxiety	cericlamine		Jouveinal
		SSRI	Depression	Lu 35-138		Lundbeck
		SSRI	Depression / OCD / Pain	LY 214,281		Lilly
		SSRI	Depression	LU AA 21-004		Lundbeck
		SSRI	Depression / Anxiety	cyanodothiepine		?
		SSRI	Depression / Anxiety	ademethionine / s-adenosylmethionine		Sempi-Gilbpharma
		SSRI	Depression / Anxiety	YM 992		Yamanouchi
Peptidergic Transmitter System	93	Substance P receptor (NK1) antagonist	Depression / Anxiety	aprepitant	40 to 160mg daily	Merck
		Substance P receptor (NK1) antagonist	Depression / Anxiety	TAK-637		Takeda/Abbott
		Substance P receptor (NK1) antagonist	Depression / Anxiety	GW597599		GlaxoSmithKline
		Substance P receptor (NK1) antagonist	Depression / Anxiety	vestipitant		GlaxoSmithKline
		Substance P receptor (NK1) antagonist	Depression / Anxiety	CP-122,721		Pfizer
		Substance P receptor (NK1) antagonist	Depression / Anxiety	R673		Roche
		Substance P receptor (NK1) antagonist	Depression / Anxiety	GW679769		GlaxoSmithKline
		Substance P receptor (NK1) antagonist	Depression / Anxiety	GW823296		GlaxoSmithKline
		Substance P receptor (NK1) antagonist	Depression / Anxiety	679769		GlaxoSmithKline
		Substance P receptor (NK1) antagonist	Depression / Anxiety	823296		GlaxoSmithKline
Other / Unknown	94	sulfonamide	Mania	zonisamide	100 to 600mg daily	Elan Pharmaceuticals
Peptidergic Transmitter System	95	tachykinin antagonists	Depression / Anxiety	SR 48968	unknown	Sanofi-Synthelabo
Other / Unknown	96	unknown	Alzheimer's Disease	DP-543	unknown	Bristol-Myers Squibb
		unknown	Depression	R226060 (YKP-10A)	unknown	Johnson & Johnson Pharmaceutical
		unknown	Parkinson's Disease	[illegible]	unknown	IVAX
		unknown	Premenstrual Syndrome	ORG 33479/PH80	unknown	Organon
		unknown	Depression	ORG 34167		Organon
		unknown	Depression	CJ-017,493		Pfizer
Endocrine System	97	V1B antagonist	Depression / Anxiety	SSR149415		Sanofi-Synthelabo
Inhibitory Amino Acid System	98	modulator	Depression / Anxiety	Pregabalin	50 to 600mg daily	Pfizer
		modulator	Pain	Pregabalin	50 to 600mg daily	Pfizer
		modulator	Insomnia	PD-200,390		Pfizer
Other / Unknown	99	vomeropherin	Anxiety, Acute	PH94B		Pherin Pharmaceuticals
PHARMACOLOGICAL GROUPS: COMPOUNDS WORKING ON THE						
Amino Acid Transmitter System						
Monoaminergic Transmitter System	1					
Excitatory Amino Acid System	2					
Inhibitory Amino Acid System	3					
Peptidergic Transmitter System	4					
Adenosine Transmitter System	5					
Endocrine System	6					
Enzymatic System	7					
Nerve Cell Function System						
Neurotrophic System	8					
Neuroimmunophilin System	10					
Pathogenic Mechanisms of Dementia of the Alzheimer Type	11					
Other / Unknown Systems	12					

Examples

Example 1; Measuring pKi values of test compounds

In Table 1, the pKi values of test compounds are given for each of the dopamine receptors, 5HT receptors, adrenergic receptors and the histamine1 receptor. The affinity of test compounds for the respective receptors has been performed according to conventional procedures known in the art.

An indication "0" means that no affinity has been measured between the test compound and the receptor.

The columns displaying the pKi values for the D4 and the 5-HT2A receptor are filled with dark grey. pKi values between 8 and 9 and higher than 9 are represented by light grey boxes.

Example 2: Foregoing pipamperon-citalopram treatment in major depressive disorder: a placebo and active controlled period finding clinical trial

Table 2 represents the set-up of a clinical trial comprising for treatment groups:

Group Plc – Active / Day 0 represents the group receiving 10 mg citalopram, twice a day, starting the first day (Day 0) of active treatment in the clinical trial. This administration regime is also indicated as the mono therapy.

Group Pip - Active / Day 0 represents the group receiving a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the first day (Day 0) of active treatment in the clinical trial. This administration regime is also indicated as the non-foregoing combo therapy.

Group Pip - Active / Day 4 represents the group receiving 4 mg pipamperon, twice a day, starting the first day (Day 0) of active treatment in the clinical trial, followed by a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the fifth (Day 4) day of active treatment in the clinical trial. This administration regime is also indicated as the foregoing therapy with combination therapy starting after 4 days of active treatment.

Group Pip - Active / Day 7 represents the group receiving 4 mg pipamperon, twice a day, starting the first day (Day 0) of active treatment in the clinical trial, followed by a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the eight (Day 7) day of active treatment in the clinical trial. This administration regime is also

indicated as the foregoing therapy with combination therapy starting after 7 days of active treatment.

All subjects also undergo a placebo (PLC) run-in therapy, administered during a period of about 7 days before the active treatment starts.

During daily (D), weekly (W) or monthly (M) visits, several parameters are measured.

Under NECT is to be understood: Neuronal E-clinical Trial = Vesalius Expert development for this trial which includes the bottom-up measurement of:

- In- and exclusion-criteria
- Functional status evaluation
- Medical history
- (Pre-)treatment signs & symptoms
- DSM-IV rules for diagnosis & efficacy
- HDRS-28 (Hamilton Depression Rating Scale - 28 items)
- Medical resource utilisation
- Pre-trial & Concomittant medication
- Drug administration
- (Serious) Adverse events
- Admission to the acute and extension phase of treatment
- Right flow of the trial

Example 3: combo pipamperon-citalopram: therapeutic use in Major Depression

Purpose

Pipamperon (1'-[3-(p-Fluorobenzoyl)propyl]-[1,4'-bipiperidine]-4'-carboxamide), the active ingredient of Dipiperon (Janssen-Cilag B.V), administered to patients in a dose ranging between 8 and 12 mg is claimed via its specific pharmacological properties to be a booster of the antidepressant effect of the selective serotonin re-uptake inhibitor citalopram. Preferably, pipamperon is administered daily at least 4-5 days before administering said antidepressant. The mechanism of boosting of pipamperon has to deal with (i) the selective affinity for the dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors, and (ii) the selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors. This semi-naturalistic open label study investigated the efficacy and tolerability of the combo pipamperon - citalopramin the treatment of patients with major depression.

Details

Design:	Semi-naturalistic i.e. inclusion of every 'natural' patient in an outpatient practice but without concomitant use of mood enhancing drugs, open label
Control:	No
Phase:	Phase IIa – preliminary Proof of Concept
Location:	Belgium – Research Centre ANIMA, Alken
End Points :	Assessment scale scores, Hamilton Depression Rating Scale 17 items, Reduction, Response, Remission
Medication:	Exclusion of mood stabilisers, antipsychotics (typical and atypical) and other antidepressants

Subjects

Type	No.	Sex	Age
Patients	23	10 male & 13 female	23-80 (mean 47) years

Characteristics: patients had a major depressive disorder according to DSM-IV criteria, with or without a chronic course and a treatment refractory state towards another SSRI then citalopram.

Treatments

PIP-CIT[1] add-on: citalopram from day minus 60-20 – pipamperon from DAY 0

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon[1] Citalopram[1]	+ Pip.: 8-12 mg/day – Cit.: 20-40 mg/day	PO	bid	8 weeks

1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

PIP-CIT[1] fore-going 1-5: pipamperon from day 0 –.cital from day 1-5

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon[1] Citalopram[1]	+ Pip.: 8-12 mg/day – Cit.: 20-40 mg/day	PO	bid	8 weeks

1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

PIP-CIT[1] fore-going 6-8: pipamperon from day 0 – citalopram from day 6-8

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon[1] Citalopram[1]	+ Pip.: 8-12 mg/day – Cit.: 20-40 mg/day	PO	bid	8 weeks

1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

Results

	PIP-CIT add-on	PIP-CIT foregoing	
	After 20-60 DAYS (mean 33) (n = 5)	1-5 DAYS (mean 4) (n = 15)	6-8 DAYS (mean 7) (n = 3)
Mean Used Medication			
Pipamperone	9mg/day	10mg/day	11mg/day
Citalopram	30mg/day	26mg/day	30mg/day
Depression scale scores			
HDRS 17-item total score			
baseline	29	23	28
endpoint (week 8)	4	5	11
diminishment at week 8	-25 (+8/-9)	-18 (+8/-8)	-17 (+17/-17)
% reduction at week 8	86 (+14/-12)	80 (+20/-30)	61 (+39/-61)
response[1] at week 8	5 (100%)	15 (100%)	2 (67%)
remission[2] at week 8	4 (80%)	10 (67%)	1 (33%)

1. Response = ≥50% reduction in HDRS 17-item score;
2. Remission = HDRS 17-item score < 8

Notably, the results obtained are highly significant since the variability in every group is distributed evenly around the mean.

Add-on PIP-CIT

Figure 1 schematically depicts the "add-on" treatment with pipamperon 8-12 (mean 9) mg (bid) after treatment with citalopram 10-20 (mean 30) mg (bid) during 20-60 (mean 33)

days (PIPCIT ADD-ON) with HDRS-17. Totalscore is 29 at baseline in MDD in comparison with the standard efficacy of antidepressants in clinical trials according to Khan *et al.* (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

Figure 2 schematically depicts the HDRS-17 change from baseline in the combo pipamperon as "add-on" to citalopram vs SNRI (duloxetine) in Major Depression. Treatment with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n=5). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Figure 3 schematically depicts the remission rates (HDRS-17 <=7) with the combo pipamperon as "add-on" to citalopram vs SNRI (venlafaxine) vs SSRIs vs placebo in Major Depression. Treatment with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n=5). Treatment with the SNRI venlafaxine is acording to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241).Treatment with SSRIs is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with placebo is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241).

<u>Fore-going 1-5 PIP-CIT</u>

Figure 4 schematically depicts the "fore-going" treatment during 1-5 (mean 4) days with pipamperon 8-12 (mean 10) mg (bid), followed with the combination treatment of pipamperon and citalopram 20-50 (mean 26) mg/day (bid) (PIPCIT FG 1-5) in MDD (HDRS-17 at BL = 23) in comparison with the standard efficacy of antidepressants in clinical trials according to Khan *et al.* (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

Figure 5 schematically depicts the HDRS-17 change from baseline in the combo pipamperon-citalopram treatment with a "fore-going" treatment of 4 days with pipamperon (10 mg/day) vs SNRI (duloxetine) in Major Depression. Treatment with the combo pipamperon-citalopram with pipamperon 8-12 (mean 10 mg/day) (bid) 1-5 (mean 4) days before treatment with SSRI (n=15). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Figure 6 schematically depicts the remission rates (HDRS-17 <=7) with the combo pipamperon with a "fore-going" treatment of 4 days with pipamperon (10 mg/day) vs SNRI (venlafaxine) in Major Depression. Treatment with the combo pipamperon-citalopram was with pipamperon 8-12 (mean 10 mg/day) during 1-5 (mean 4) days before treatment with the SSRI (n=5). Treatment with the SNRI venlafaxine is acording to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241).Treatment with SSRIs is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with placebo is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241).

Fore-going 6-8 PIP-CIT

Figure 7 schematically depicts the "fore-going" treatment during 6-8 (mean 7) days with pipamperon 8-12 (mean 11) mg/day (bid), followed with the combination treatment of pipamperon and citalopram 20-40 (mean 30) mg/day (bid) (PIPCIT FG 6-8) in MDD (HDRS-17 at BL = 28) in comparison with the standard efficacy of antidepressants in clinical trials according to Khan *et al.* (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

Figure 8 schematically depicts the HDRS-17 change from baseline in the combo pipamperon-citalopram treatment with a "fore-going" treatment of 7 days with pipamperon (11 mg/day) vs SNRI (duloxetine) in Major Depression. Treatment with the combo pipamperon-citalopram with pipamperon 8-12 (mean 11 mg/day) (bid) 6-8 (mean 7) days before treatment with SSRI (n=3). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Comparison "add-on" vs "fore-going"

Figure 9 schematically depicts a comparison between "fore-going" and "add-on" treatments with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in MDD in comparison with the standard efficacy of antidepressants in clinnical trials according to Khan *et al.* (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

Figure 10 schematically depicts a comparison between "fore-going" and "add-on" treatments. In particular, the HDRS-17 change from baseline between "fore-going" and "add-on" treatment with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SNRI duloxetine in Major Depression is depicted. Treatment with the combo pipamperon as "add-on" to citalopram, with pipamperon 8-12 mg/day (mean 9 mg/day) 20-60 (mean 33) days after treatment with the SSRI (n=5). Treatment with the combo pipamperon-citalopram, with pipamperon 8-12 mg/day (mean 11 mg/day; bid) 6-8 days (mean 7 days) before treatment with the SSRI (n = 15). Treatment with the combo pipamperon-citalopram, with pipamperon 8-12 mg/day (mean 10 mg/day; bid) 1-5 days (mean 4 days) before treatment with the SSRI (n = 15). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Figure 11 schematically depicts the remission rates (HDRS-17 <=7) in a comparison between "fore-going" and "add-on" treatment with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SNRI venlafaxine in Major Depression. Treatment with the combo pipamperon-citalopram was with pipamperon 8-12 (mean 10 mg/day) during 1-5 (mean 4) days before treatment with the SSRI (n = 15). Treatment with the SNRI venlafaxine is acording to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with pipamperon as "add-on" to citalopram, with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n = 5).

The intention-to-treat / last-observation-carried-forward analysis showed a high therapeutic efficacy according HDRS 17-item in all the treatment groups. This was especially true for the 'add-on' group probably caused by the longer treatment with an active antidepressant (+33 days). The huge therapeutic effect observed in the 'PIP-CIT 1-5' group present for at a mean dosage of pipamperon of 10 mg per day and administered the first four days of treatment without an active antidepressant, indicates the boosting effect of pipamperon on the SSRI citalopram at an extremely and thus unconventional low dose. Only 1 patient discontinued treatment due to a lost of follow-up.

Adverse Events

Side effects (patients)	PIP-CIT add-on After 20-60 DAYS (mean 33) (n = 5)	PIP-CIT foregoing 1-5 DAYS (mean 4) (n = 15)	6-8 DAYS (mean 7) (n = 3)
Discontinued treatment due to adverse events	0	0	0
By system:			
body as a whole	0	0	0
central and peripheral nervous system	1(20%)	4(26.6%)	0
gastrointestinal	1(20%)	5(33%)	2(66.6%)
musculoskeletal	1(20%)	3(20%)	0
psychiatric	0	0	0
respiratory	0	1(6.6%)	0
skin and appendages	1(20%)	2(13.3%)	1(33.3%)
vascular	0	1(6.6%)	0
urinary	0	1(6.6%)	0

Laboratory parameters, ECG, bodyweight and vital signs were not measured since this was a naturalistic study.

Assessment

Outcome

Efficacy: the 4-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day is comparable to the add-on combo pipamperon-citalopram.

Efficacy: the 4-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day is larger than the 7-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day.

Efficacy: the combo pipamperon 8-12mg/d - citalopram 20-40mg/day is larger than the in the art known antidepressants SSRIs.

Tolerability

Tolerability: the 4-day fore-going treatment is comparable to the 7-day fore-going combo is comparable to add-on combo pipamperon-citalopram.

Tolerability: no discontinued treatment due to adverse events.

Study Messages

The boosting effect of pipamperon at an extremely unconventional low dose on a SSRI is indicated since the efficacy of the 'add-on' and '4-day fore-going' combo 'pipamperon 8 -12 mg/d - citalopram 20 - 40 mg/day' is in this study as twice higher as known in the art in the treatment of patients with major depression.

The combo pipamperon-citalopram is generally well tolerated in patients with depression i.e. at least no specific added adverse events were occurring by adding pipamperon at the doses used in the study.

Example 4: combo pipamperon-citalopram: therapeutic use in Obsessive-Compulsive Disorder (OCD).

Purpose

Pipamperon (1'-[3-(p-Fluorobenzoyl)propyl]-[1,4'-bipiperidine]-4'-carboxamide), the active ingredient of Dipiperon (Janssen-Cilag B.V), administered to a patient in a dose ranging between 8 and 12 mg is claimed via its specific pharmacological properties to be a booster of the effect of the selective serotonin re-uptake inhibitor citalopram towards OCD. Preferably, pipamperon is administered daily at least 4-5 days before administering said antidepressant. The mechanism of boosting of pipamperon has to deal with (i) the selective affinity for the dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) the selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors. This semi-naturalistic open label study investigated the efficacy and tolerability of the combo pipamperon - citalopram in the treatment of patients with OCD.

Details

Design:	Semi-naturalistic i.e. inclusion of every 'natural' patient in an outpatient practice but without concomitant use of mood enhancing drugs, open label
Control:	No
Phase:	Phase IIa – preliminary Proof of Concept
Location:	Belgium – Research Centre ANIMA, Alken
End Points :	Assessment scale scores, Yale-Brown Obsessive-Compulsive Scale, Reduction, Remission
Medication:	Exclusion of mood stabilisers, antipsychotics (typical and atypical) and other antidepressants

Subjects

Type	No.	Sex	Age
Patients	7	1 male & 7 female	20-63 (mean 33) years

Characteristics: patients had an obsessive-compulsive disorder according to DSM-IV criteria, with or without a chronic course and a treatment refractory state towards another SSRI then citalopram.

Treatments

PIP-CIT[1] ADD-ON: citalopram from DAY minus 730-60 – pipamperon from DAY 0

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperone[1] + Citalopram[1]	Pip.: 8-16 mg/day – Cit.: 30-80 mg/day	PO	bid	12 weeks

1. Pipamperone (Pip) and Citalopram (Cit) dosage was adjusted according to clinical response.

PIP-CIT[1] FORE-GOING 4-6: pipamperon from DAY 0 – citalopram from DAY 4-6

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperone[1] + Citalopram[1]	Pip.: 8-16 mg/day – Cit.: 30-80 mg/day	PO	bid	12 weeks

1. Pipamperone (Pip) and Citalopram (Cit) dosage was adjusted according to clinical response.

Results

	PIP-CIT add-on after 730-60 DAYS (mean 241) (n = 6) with mean Cit. 54mg/d and Pip. 11mg/d PIP-CIT foregoing 4-6 DAYS (mean 5) (n = 2) with mean Cit. 60mg/d and Pip. 10mg/d
Y-BOCS score	
Baseline	
Total	31
Obsessions	18
Compulsions	13
Endpoint (week 12)	
Total	15
diminishment	-16 (+16/-11)
% reduction	53
Obsessions	
total	8
diminishment	-10 (+9/-7)
% reduction	57
Compulsions	
total	7
diminishment	-6 (+7/-6)
% reduction	45
% Remission	
YBOCS score ≤8	29
BOCS score ≤16	57

Notably, the results obtained are highly significant since the variability in every group is distributed evenly around the mean.

Figure 12 schematically depicts the Y-BOCS total score: "fore-going" and "add-on" treatment with pipamperon (8-15 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-

citalopram (n = 7). Treatment with fluvoxamine (controlled release) mean 271 mg/day (n = 253) is according to Hollander et al. (2003).

Figure 13 schematically depicts the Y-BOCS obsession score: "fore-going" and "add-on" treatment with pipamperon (8-15 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-citalopram (n = 7). Treatment with fluvoxamine (controlled release) mean 271 mg/day (n = 253) is according to Hollander et al. (2003).

Figure 14 schematically depicts the Y-BOCS compulsion score: "fore-going" and "add-on" treatment with pipamperon (8-16 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-citalopram (n = 7). Treatment with fluvoxamine (controlled release) mean 271 mg/day (n = 253) is according to Hollander et al. (2003).

The intention-to-treat / last-observation-carried-forward analysis showed a high therapeutic efficacy according Y-BOCS total score, obsession and compulsion scores. This indicates the boosting effect of pipamperon on the SSRI citalopram at an extremely and thus unconventional low dose. No patient discontinued treatment.

Assessment

Efficacy: the combo pipamperone 8-16mg/d - citalopram 30-80mg/day > the in the art known compounds effective towards OCD (Hollander E, Koran LM, Goodman WK, Greist JH, Ninan PT, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. Journal of Clinical Psychiatry 64: 640-647, Jun 2003 Mount Sinai School of Medicine, New York, New York, USA; Solvay Pharmaceuticals Inc., Marietta, Georgia, USA).

Study Messages

The boosting effect of pipamperon at an extremely unconventional low dose on a SSRI is indicated since the efficacy of the 'add-on' and 'fore-going' combo 'pipamperon 8-15 mg/d - citalopram 30-80 mg/day' is in this study as twice higher as known in the art in the treatment of patients with obsessive-compulsive disorder.

Example 5: combo pipamperon-citalopram: therapeutic use in Panic Disorder.

Purpose

Preliminary examination of a "fore-going" and "add-on" treatment with pipamperon and citalopram in comparison with the SSRI in Panic Disorder.

Results

The results are indicated in Figure 15. Figure 15 schematically depicts the CGI-severity score: "fore-going" and "add-on" treatment with pipamperon (8 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SSRI in Panic Disorder. Treatment with the combo pipamperon-citalopram (n = 3). Treatment with paroxetine is according to the Journal of Clinical Psychiatry (2004) 65: 405-413. Treatment with Sertraline is according to the Journal of Clinical Psychiatry (2004) 65: 405-413.

Conclusion

Notably, although a small test group has been used (n = 3), the distribution around the mean is good. It will further be apparent from Figure 15 that the effect of the combo treatment of pipamperon and citalopram is twice as high as the standard treatments with paroxetine or sertraline.

Example 6: POC process for mayor depressive disorder

Concept: Combo of the high selective 5-HT2A/D4 antagonist pipamperon with:

- a compound active towards the Amino Acid Transmitter, Peptidergic Transmitter, Adenosine Transmitter, Endocrine and/ or Enzymatic System;
- a fore-going admission during 4 days of pipamperon;
- a dose of pipamperon of 12 mg/day

Objectives: Demonstrating that this combo ~~therapy has~~:

- the potency of being a treatment standard for depression by having an added value of reducing the total score of the Hamilton Depression Rating Scale – 17 items (HDRS-17) after 8 weeks of therapy with a least 20% more than reached with the conventional known antidepressants, *i.e.* 60% versus 40%. This stands for an added medium demission of 5 points on the total score of the HDRS-17 and by this will be very highly

significant since the mean difference in all recent clinical trials between placebo and active treatment is 2.5;

- a more sustained therapeutic effect than the conventional mono therapy by preventing significant more relapses during 48 weeks following the acute treatment; and/or
- a complete neutral safety profile, e.g. there are no more adverse events in the combo therapy then in mono admission of the in the combo used antidepressant compound.

Process: the following different steps were implemented to reach out for these objectives (see also Tables 3 and 4):

(1) an naturalistic open label study (n=>20) on a depressive population with a normal variability of medical and psychiatric history, course of depression, earlier and concomitant therapy admitting the golden standard antidepressant citalopram 20-40 mg/day and a dose of 8-12 mg/day of pipampéron in a foregoing, simultaneous or add-on use.

(2) a 16 weeks placebo controlled randomised four armed study of each 36 patients with a mayor depressive disorder admitting:

- from day 0: placebo or pipamperon (PIP) 10 mg/day or an active antidepressant compound or the combination of the last two;
- from day 4: placebo or pipamperon 10 mg/day combined with an active antidepressant compound or an active antidepressant compound without pipamperon.

By including rigorous control groups (placebo and active comparator; see Tables 3 and 4) this clinical trial is evaluated as a proof of concept of the added value of the combo and the foregoing treatment method since the inclusion/exclusion of:

- a negative trial, i.e. no significant difference between the placebo and active treatment with the comparator;
- a failed trial, i.e. no significant difference between the active and the studied treatment i.e. the combo.

(3) an active controlled randomised relapse prevention study following the POC trial during another 36 weeks with three arms of each 36 patients which is formed by:

- continuation of the active mono therapy;
- randomising the patients with a combo therapy in a group with an active mono therapy and with a continuation of the combo treatment.

Claims

1. Use of pipamperon for the preparation of a medicament for treating a disease or disorder with an underlying dysregulation of the emotional functionality, wherein said pipamperon is administered to a patient in a dose ranging between 5 and 15 mg of the active ingredient, and wherein a second compound is administered simultaneously with, separate from or sequential to said pipamperon to augment the therapeutic effect of said second compound.

2. Use according to claim 1, wherein said pipamperon is administered daily at least one day before administering said second compound.

3. Use according to any of claims 1 to 2, wherein said second compound affects the monoaminergic tansmitter system.

4. Use according to claim 3, wherein said second compound is selected from the group comprising: 5-HT reuptake enhancer (1), 5-HT1 autoreceptor agonist (2), 5HT1A receptor agonist (3), 5-HT1A receptor antagonist (4), 5-HT1B receptor antagonist (5), 5-HT2B receptor antagonist (6), 5-HT2C receptor antagonist (7), 5-HT3 receptor antagonist (8), 5-HT6 receptor antagonist (9), adrenergic transmitter releaser (12), α1 adrenoreceptor antagonist (13), α2 adrenoreceptor antagonist (14), β3 adrenoreceptor agonist (19), cannabioid receptor antagonist (21), D1 receptor agonist (27), D2 receptor antagonist (28), D3 receptor antagonist (29), DA uptake inhibitor (30), dopamine receptor agonist (31), H3 receptor antagonist (42), compounds which increase brain concentrations of 5-HT (44), levodopa (48), MAO reuptake inhibitor (50), MAO-A & MAO-B reuptake inhibitor (51), MAO-B inhibitor (52), MAO-B re-uptake inhibitor (53), NARI (60), NaSSA (61), NDRI (62), RIMA (82), SDA (84), SDRI (85), Second messenger beta agonist (86), SNDRI (90), SNRI (91) and SSRI (92).

5. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial

behaviour, bereavement, occupational problem and problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

6. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1 autoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1 autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

7. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A) receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin) 1A receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

8. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

9. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1B receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1B receptor

antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2B receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2B receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

11. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2C receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2C receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

12. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance-related disorders, characterized in that pipamperon or said pharmaceutically

acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

13. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT6 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT6 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

14. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

16. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

17. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders,

impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

18. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, pain disorders and delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabioid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabioid receptor 1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

19. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, pain disorders and delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

21. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

22. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with,

separate from or prior to the administration of a DA (dopamine) uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA (dopamine) uptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

23. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders and problems related to abuse or neglect, pain disorder and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

24. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a histamine H3receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said histamine H3receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases brain concentrations of 5-HT (serotonin), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

26. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a levodopa/decarboylase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said levodopa/decarboylase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

27. A pharmaceutical composition comprising (a) pipamperon, and (b) a levodopa/decarboylase inhibitor compound, preferably is (eti)levodopa/carbidopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

28. A pharmaceutical composition according to claim 27, wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein

said levodopa/decarboylase inhibitor compound is levodopa/carbidopa, preferably provided in a unitary dose of between 100 mg and 10 mg of the active ingredient.

29. A pharmaceutical composition according to claim 27 or 28, wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboylase inhibitor compound is levodopa/carbidopa or etilevodopa/carbidopa in combination with entacapone, of which the latter is preferably provided in a unitary dose of between 500 mg and 100 mg of the active ingredient.

30. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of non-cognitive mental disease or disorder which are substance related disorders and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

31. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

32. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

33. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) reuptake inhibitor to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) reuptake inhibitor, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

34. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline re-uptake inhibitor (NARI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake

inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

36. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

37. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders

consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

38. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorder and delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

39. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-

related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine re-uptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine re-uptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

40. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

41. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-

deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

42. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

43. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin

re-uptake inhibitor (SSRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

44. Use according to claim 1 or 2, wherein said disease or disorder is Alzheimer disease.

45. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

46. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT6 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT6 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

47. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an acetylcholinesterase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said acetylcholinesterase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

48. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

49. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an amyloid aggregation-inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said amyloid aggregation-inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

50. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

51. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a choline uptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said choline uptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

52. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound that activates ERK (extracellular signal-related kinase) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound that activates ERK (extracellular signal-related kinase), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

53. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

54. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a histamine H3-receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said histamine H3-receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

55. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases insulin sensitivity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases insulin sensitivity, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

56. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

57. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a muscarinic receptor partial agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said muscarinic receptor partial agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

58. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

59. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable

salt thereof is administered simultaneously with, separate from nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nerve growth factor (NGF) gene therapy, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

60. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

61. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

62. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a non-steroidal anti-inflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

63. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of

Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

64. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

65. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

66. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

67. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

68. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

69. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and ~~problems~~ related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate ~~from or~~ prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

70. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

71. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

72. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep

disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

73. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

74. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable

salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

75. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

76. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a substance P receptor (NK1) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

77. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a tachykinin antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

78. Use according to any of claims 1 to 4 or 7, wherein said second compound is gepirone.

79. A method for preparing a compound having a selective D4 and 5-HT2A antagonist, reverse agonist or partial agonist activity comprising the following steps: (a) measuring the selective affinity of a test compound to the D4 receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the D4 receptor in respect to all the other D receptors, and measuring the selective efficacy of the selected compound to the D4 receptor and selecting a compounds which is a selective antagonist, inverse agonist or partial agonist of the D4 receptor; (b) measuring the selective affinity of a test compound to the 5-HT2A receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the 5-HT2A receptor in respect to all the other 5HT receptors, and measuring the selective efficacy of the selected compound to the 5-HT2A receptor and selecting a compounds which is a selective antagonist, inverse agonist or partial agonist of the 5-HT2A receptor; (c) identifying a compound which is selected in (a) and (b), (d) preparing the compound identified in (c).

80. Compound prepared by the method of claim 79.

81. Use according to any of claims 1, 2 or 7, wherein said second compound is chosen from the group consisting of fluvoxamine controlled release, phenserine tartrate,

atomoxetine hydrochloride, bupropion (controlled-release formulation), ropinirole HCL (controlled-release formulation), INN 00835, galantamine (extended release formulation), paliperidone, tomoxetine, aprepitant, rivastigmine tartrate, ORG 34517/34850, sunepitron, sumanirole, milnacipran, idazoxan, xaliproden, SR 58611, befloxatone, litoxetine, tianeptine, agomelatine, SPD 503, flesinoxan, bifeprunox, ramelteon, etilevodopa, rasagiline (TVP-1012) and desvenlafaxine.

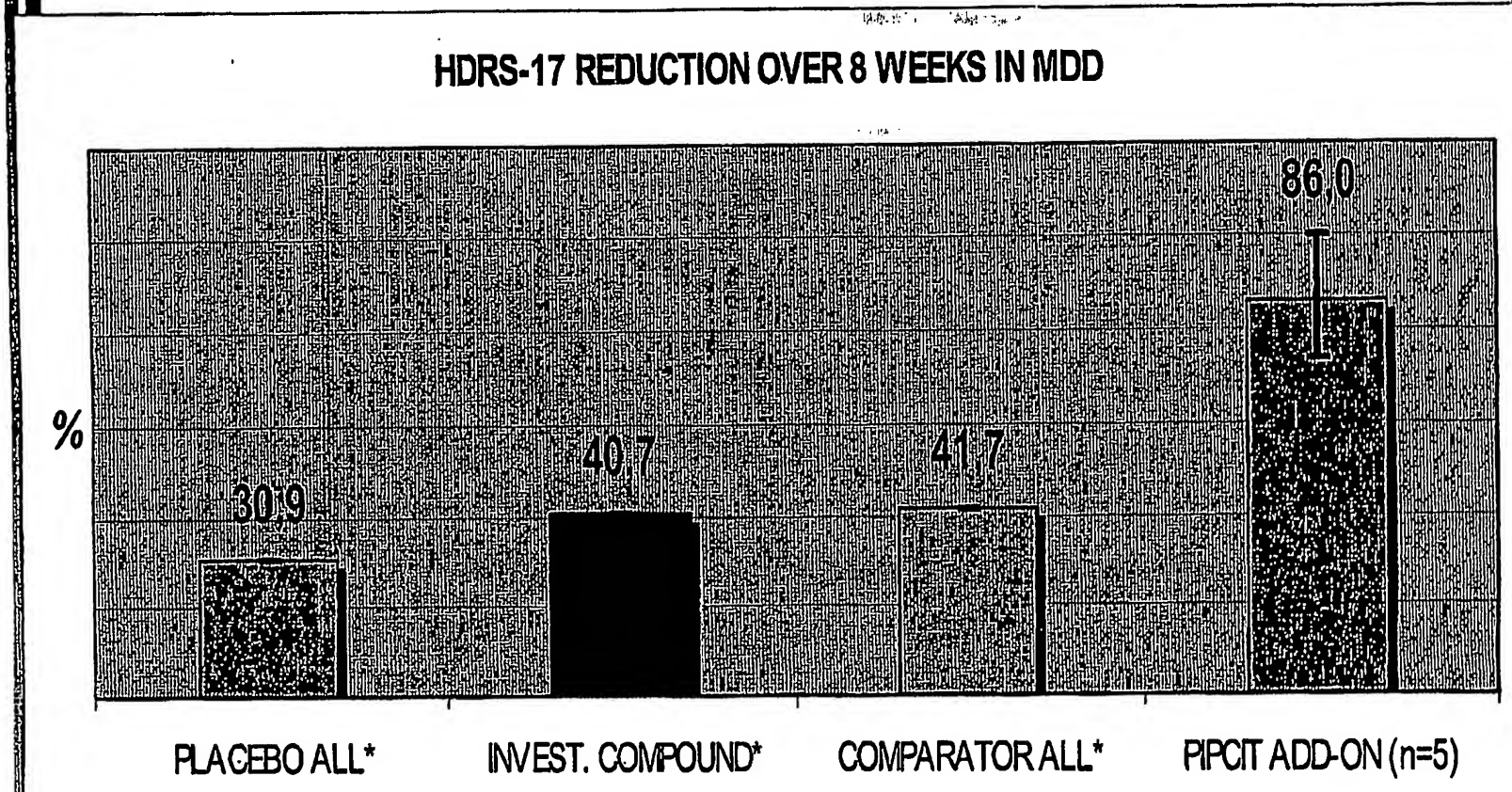
82. Use according to any of claims 1, 2 or 7, wherein said second compound is chosen from the group consisting of galantamine (extended release formulation), R121919, risperidone, paliperidone and R228060 (YKP-10A).

Abstract

The present invention relates to the use of compounds and compositions of compounds having D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity for the treatment of the underlying dysregulation of the emotional functionality of mental disorders (i.e. affect instability – hypersensitivity – hyperaesthesia – dissociative phenomena - etc). The invention also relates to methods comprising administering to a patient diagnosed as having a neuropsychiatric disorder a pharmaceutical composition containing (i) compounds having D4 antagonistic, partial agonistic or inverse agonistic activity and (ii) compounds having 5-HT2A antagonistic, partial agonistic or inverse agonistic, and (iii) any known medicinal compound and compositions of said compounds. The combined D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic effects may reside within the same chemical or biological compound or in two different chemical and/or biological compounds.

Figure 1

Add-On Treatment *with Pipamperon 8-12 (mean 9) mg (bid) after Treatment with Citalopram 10-20 (mean 30) mg (bid) during 20-60 (mean 33) days (PIPCIT ADD-ON) with HDRS-17 Totalscore = 29 at Baseline in MDD in Comparison with the Standard Efficacy of Antidepressants in Clinical Trials**



A. KHAN et al, Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials, ARCH. GP GENERAL PSYCHIATRY / VOL 57, APR 2000)

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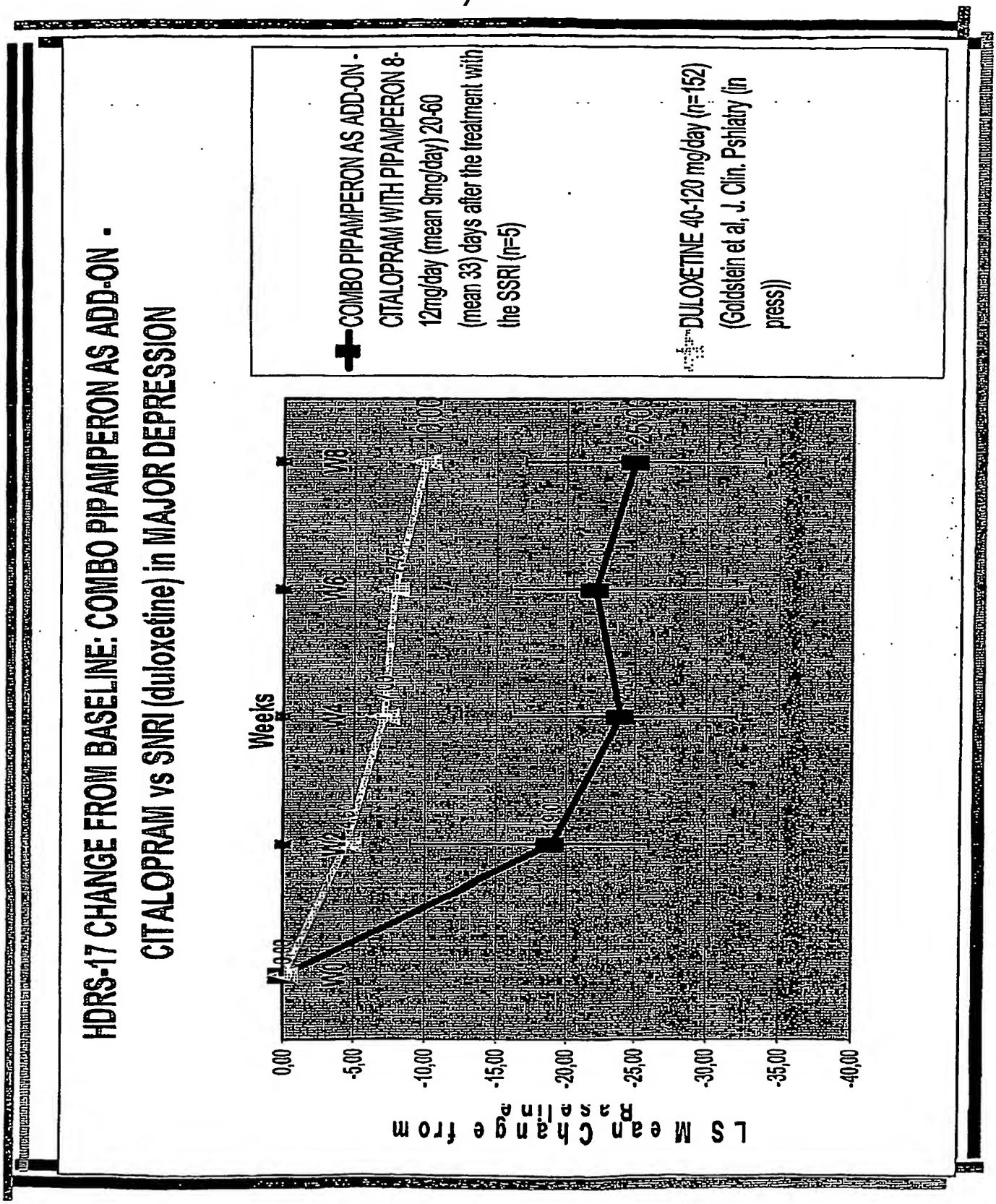
HDRS-17 CHANGE FROM BASELINE: COMBO PIPAMPERON AS ADD-ON - CITALOPRAM vs SNRI (duloxetine) in MAJOR DEPRESSION
COMBO PIPAMPERON AS ADD-ON - CITALOPRAM WITH PIPAMPERON 8-12mg/day (mean 9mg/day) 20-60 (mean 33) days after the treatment with the SSRI (n=5)
DULOXETINE 40-120 mg/day (n=152) (Goldstein et al, J. Clin. Pshiatry (in press))
LS Mean Change from Baseline
Weeks
W0
W2
W4
W6
W8
0,00
-5,00
-10,00
-15,00
-20,00
-25,00
-30,00
-35,00
-40,00

Figure 2

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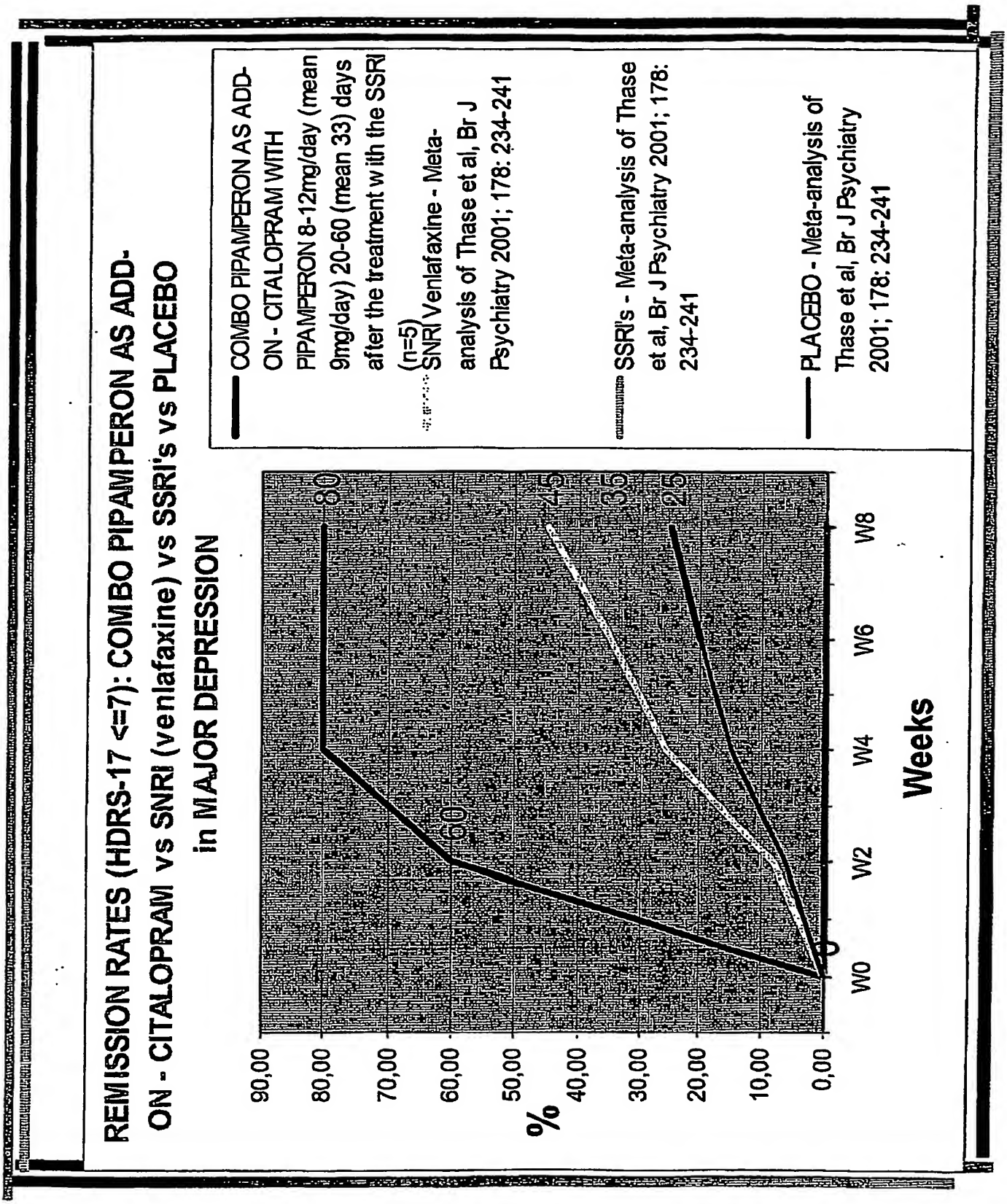
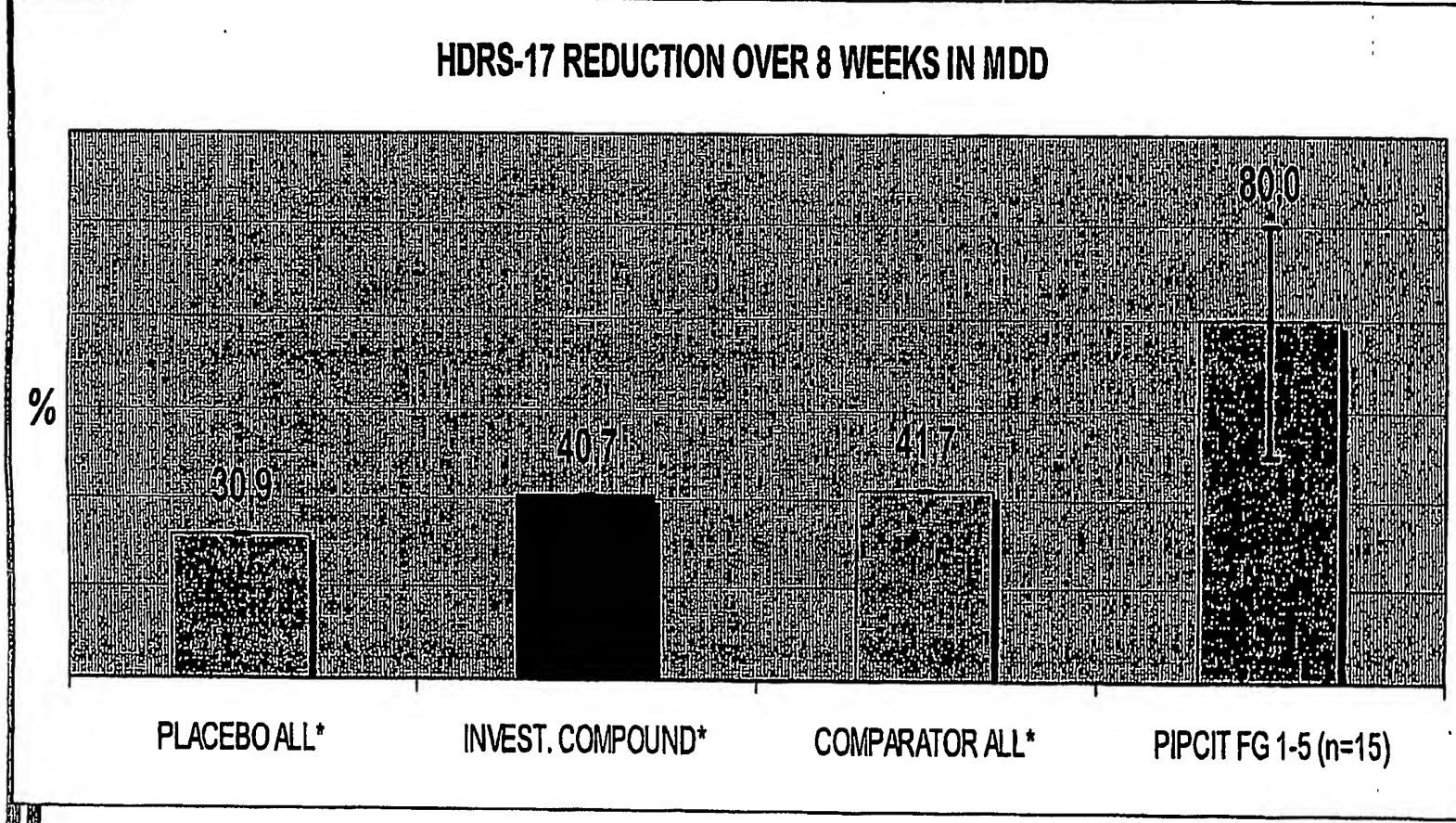

REMISSION RATES (HDRS-17 <=7): COMBO PIPAMPERON AS ADD-ON - CITALOPRAM vs SNRI (venlafaxine) vs SSRI's vs PLACEBO in MAJOR DEPRESSION
90,00
80,00
70,00
60,00
50,00
40,00
30,00
20,00
10,00
0,00
%
W0
W2
W4
W6
W8
Weeks
80
60
45
35
25
COMBO PIPAMPERON AS ADD-ON - CITALOPRAM WITH PIPAMPERON 8-12mg/day (mean 9mg/day) 20-60 (mean 33) days after the treatment with the SSRI (n=5)
SNRI Venlafaxine - Meta-analysis of Thase et al, Br J Psychiatry 2001; 178: 234-241
SSRI's - Meta-analysis of Thase et al, Br J Psychiatry 2001; 178: 234-241
PLACEBO - Meta-analysis of Thase et al, Br J Psychiatry 2001; 178: 234-241

Figure 3

Figure 4

***Foregoing Treatment During 1-5 (mean 4) days** with Pipamperon 8-12 (mean 10) mg/day (bid) Followed With the Combination Treatment of Pipamperon and Citalopram 20-50 (mean 26) mg/day (bid) (PIPCIT FG 1-5) in MDD (HDRS-17 at BL = 23) in Comparison with the Standard Efficacy of Antidepressants in Clinical Trials**



A. KHAN et al, Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials, ARCH. OF GENERAL PSYCHIATRY, VOL 57, APR 2000)

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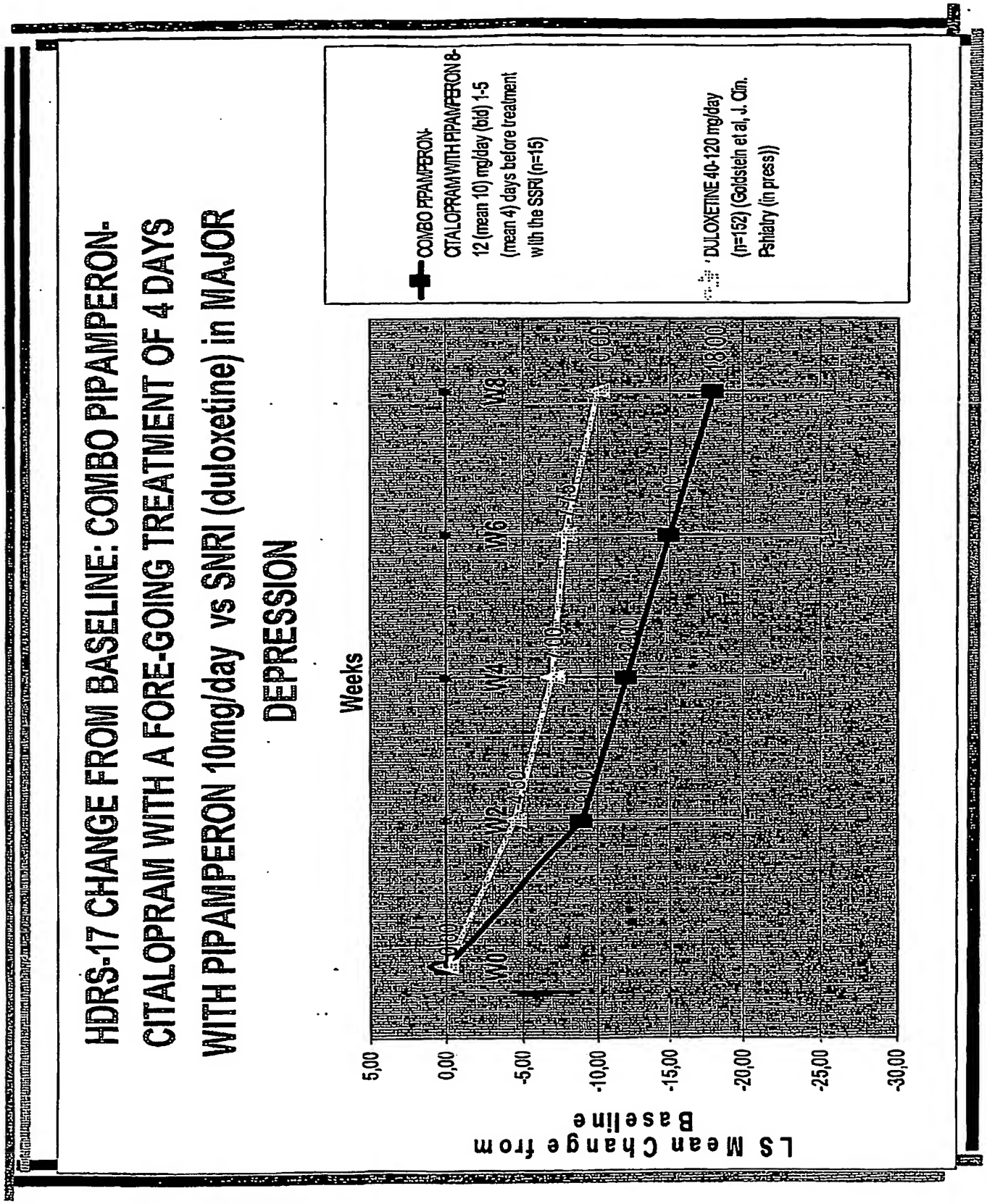
HDRS-17 CHANGE FROM BASELINE: COMBO PIPAMPERON-CITALOPRAM WITH A FORE-GOING TREATMENT OF 4 DAYS WITH PIPAMPERON 10mg/day vs SNRI (duloxetine) in MAJOR DEPRESSION
LS Mean Change from Baseline
Weeks
W0
W2
W4
W6
W8
5,00
0,00
-5,00
-10,00
-15,00
-20,00
-25,00
-30,00
COMBO PIPAMPERON-CITALOPRAM WITH PIPAMPERON 8-12 (mean 10) mg/day (bid) 1-5 (mean 4) days before treatment with the SSRI (n=15)
DULOXETINE 40-120 mg/day (n=152) (Goldstein et al, J. Clin. Psihiatry (in press))

Figure 5

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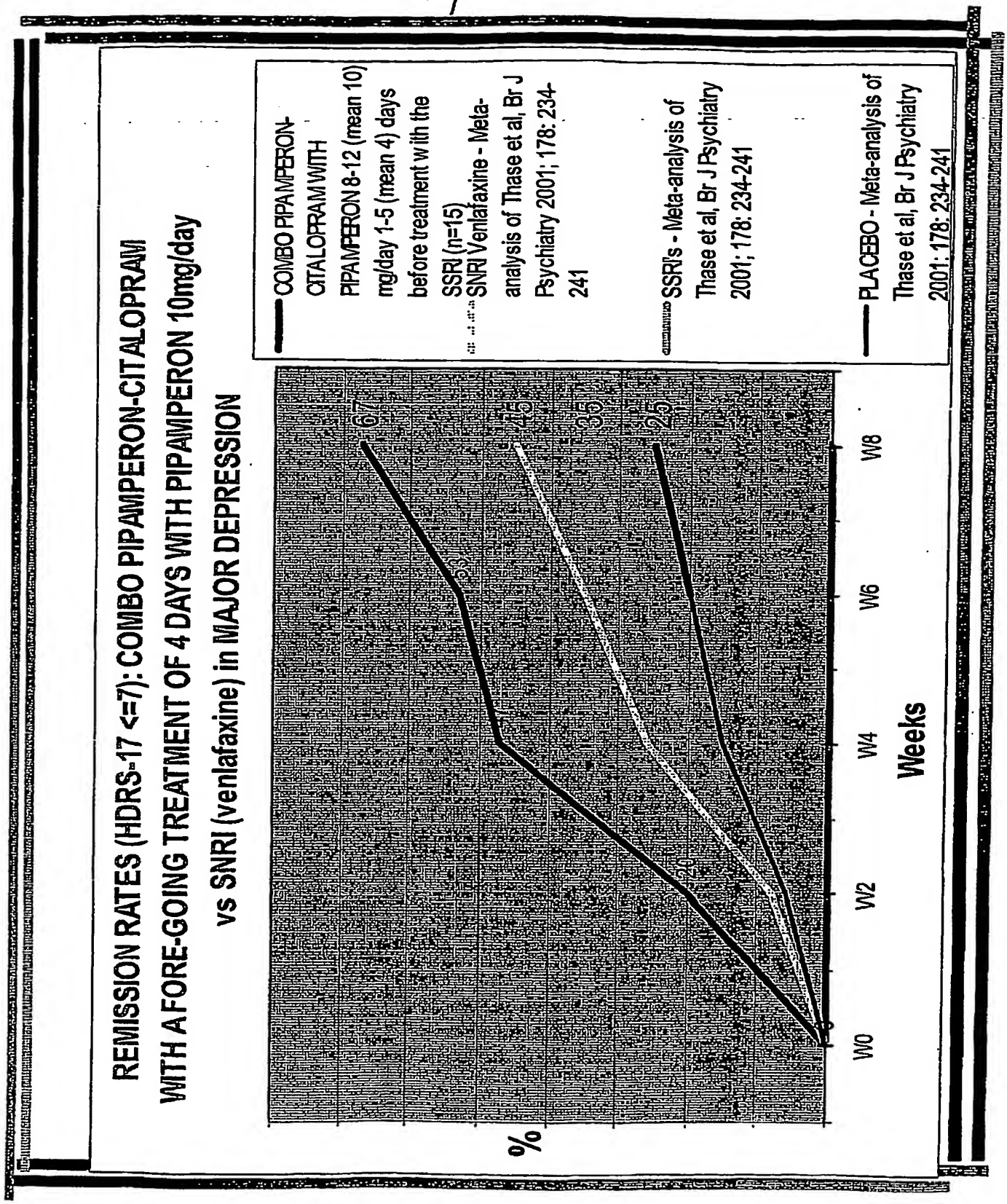
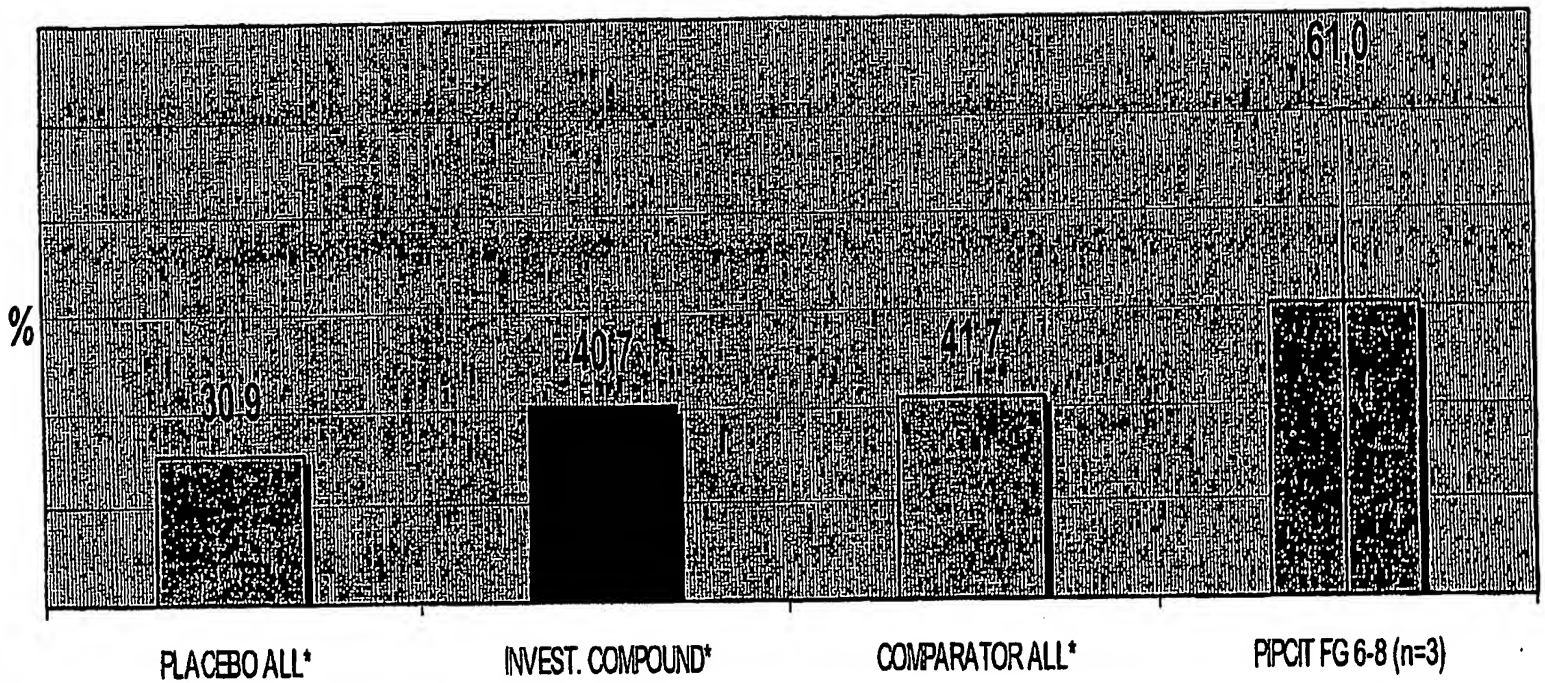

REMISSION RATES (HDRS-17 <=7): COMBO PIPAMPERON-CITALOPRAM WITH A FORE-GOING TREATMENT OF 4 DAYS WITH PIPAMPERON 10mg/day vs SNRI (venlafaxine) in MAJOR DEPRESSION
COMBO PIPAMPERON-CITALOPRAM WITH PIPAMPERON 8-12 (mean 10) mg/day 1-5 (mean 4) days before treatment with the SSRI (n=15)
SNRI Venlafaxine - Meta-analysis of Thase et al, Br J Psychiatry 2001; 178: 234-241
SSRI's - Meta-analysis of Thase et al, Br J Psychiatry 2001; 178: 234-241
PLACEBO - Meta-analysis of Thase et al, Br J Psychiatry 2001; 178: 234-241
%
67
45
35
25
W0
W2
W4
W6
W8
Weeks

Figure 6

Figure 7

***Foregoing Treatment During 6-8 (mean 7) days** with Pipamperon 8-12 (mean 11) mg/day (bid) Followed With the Combination Treatment of Pipamperon and Citalopram 20-40 (mean 30) mg/day (bid) (PIPCIT FG 6-8) in MDD (HDRS-17 at BL = 28 in Comparison with the Standard Efficacy of Antidepressants in Clinical Trials**



*A. KHAN et al, Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials, ARCH. OF GENERAL PSYCHIATRY / VOL 57, APR 2000

7 / 15

21-10-04;20:55 ;DCB EPO Munchen ;+3292802345 # E- 44

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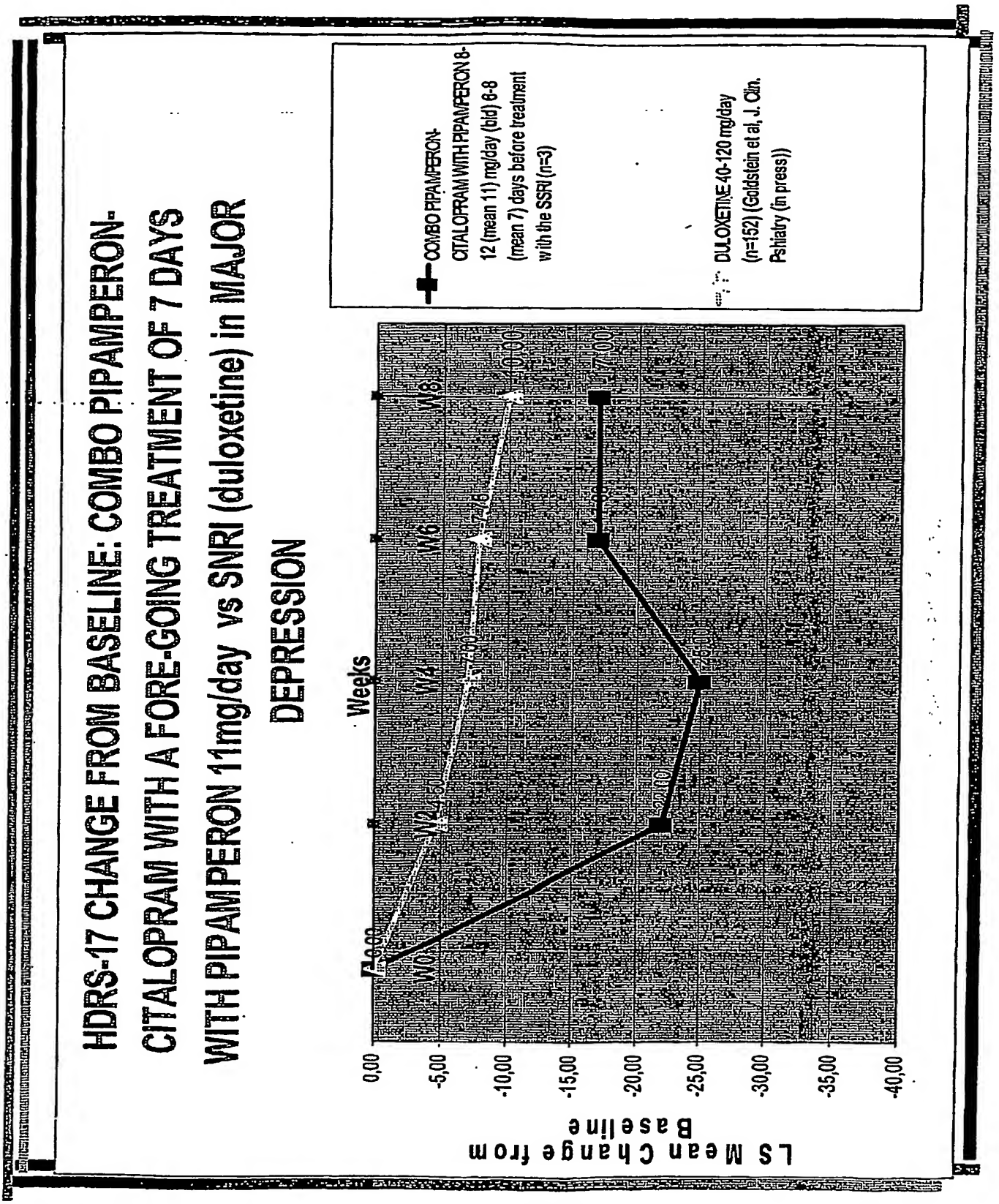
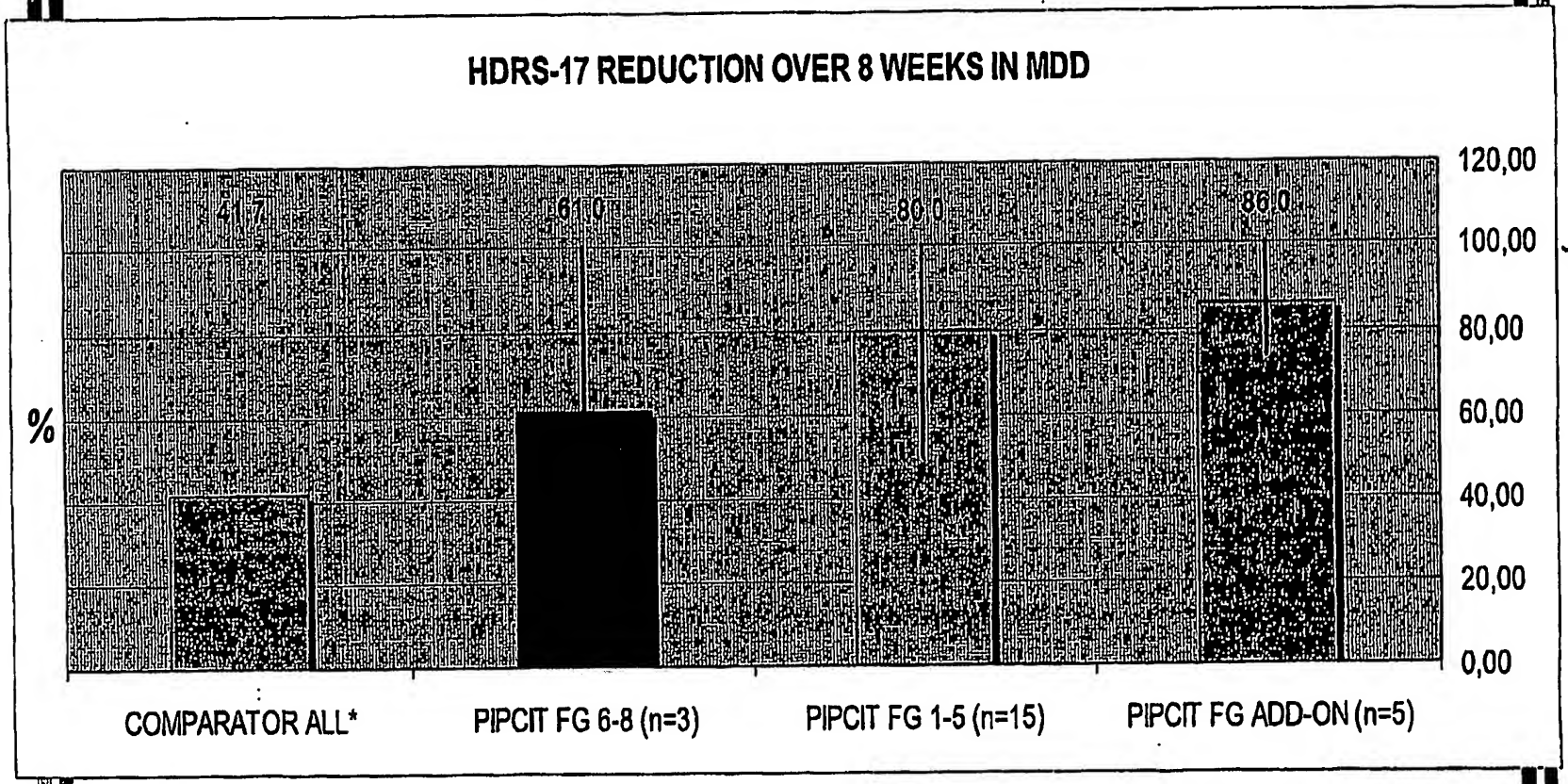

HDRS-17 CHANGE FROM BASELINE: COMBO PIPAMPERON-CITALOPRAM WITH A FORE-GOING TREATMENT OF 7 DAYS WITH PIPAMPERON 11mg/day vs SNRI (duloxetine) in MAJOR DEPRESSION
COMBO PIPAM/PERON-CITALOPRAM WITH PIPAM/PERON 8-12 (mean 11) mg/day (bid) 6-8 (mean 7) days before treatment with the SSRI (n=3)
DULOXETINE 40-120 mg/day (n=152) (Goldstein et al, J. Clin. Pshiatry (in press))
LS Mean Change from Baseline
Weeks
W0
W2
W4
W6
W8
0,00
-5,00
-10,00
-15,00
-20,00
-25,00
-30,00
-35,00
-40,00

Figure 8

Figure 3

Foregoing & Add-On Treatment *with Pipamperon 8-12 mg/day (bid) and Citalopram 20-40 mg/day (bid) in MDD in Comparison with the Standard Efficacy of Antidepressants in Clinical Trials**



* A. KHAN et al, Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials, ARCH. OF GENERAL PSYCHIATRY / VOL 57, APR 2000)

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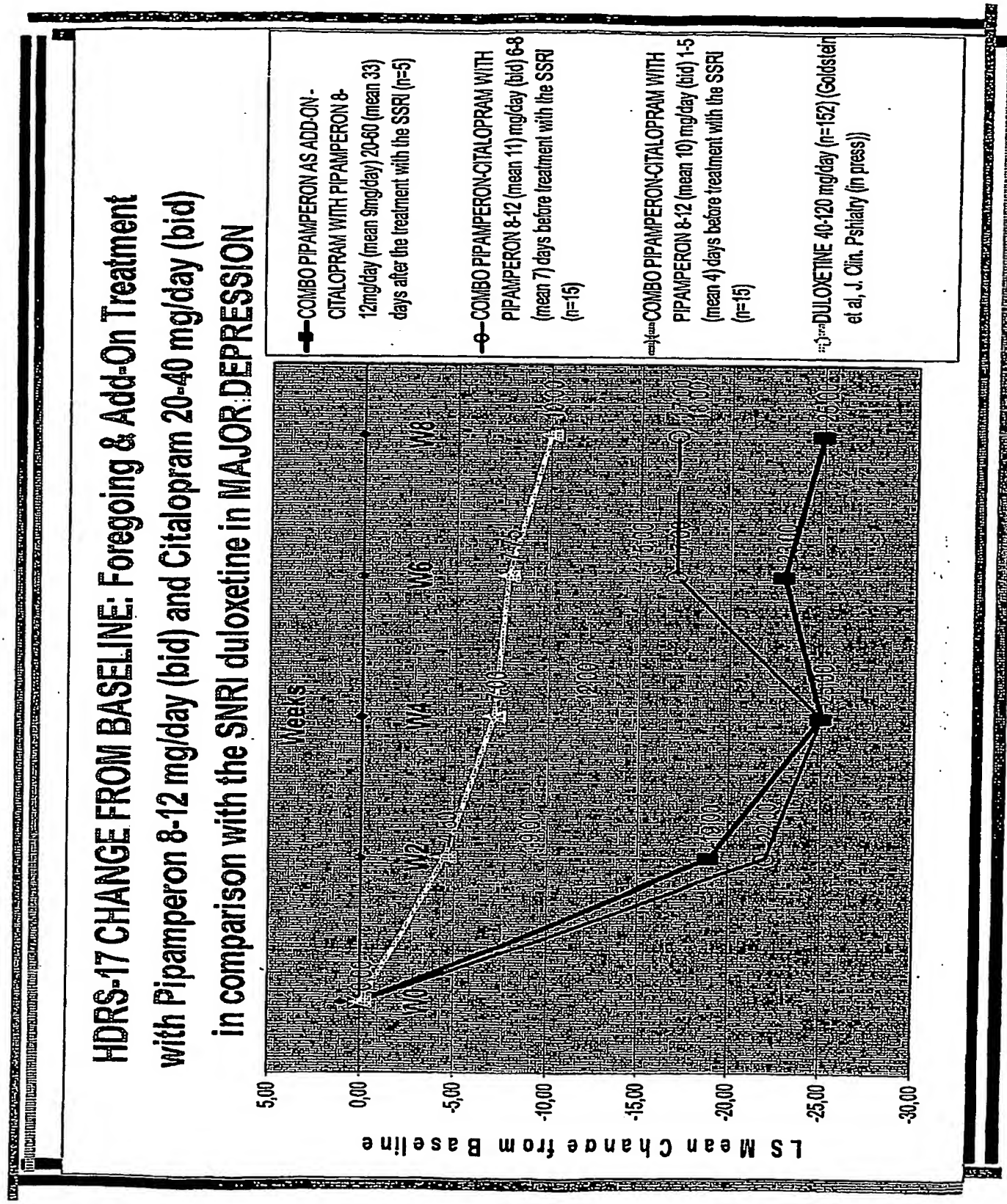
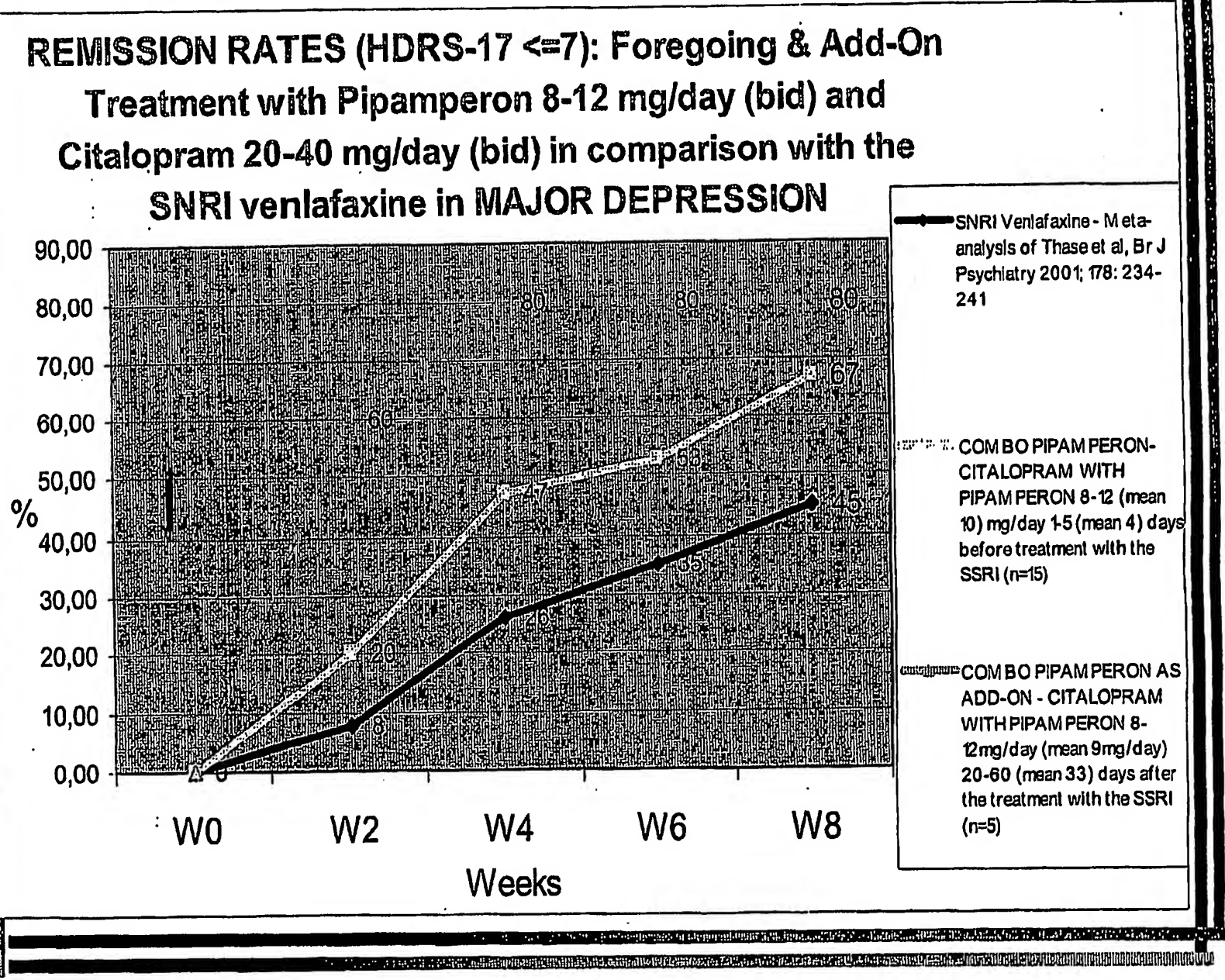


Figure 10

Figure 11



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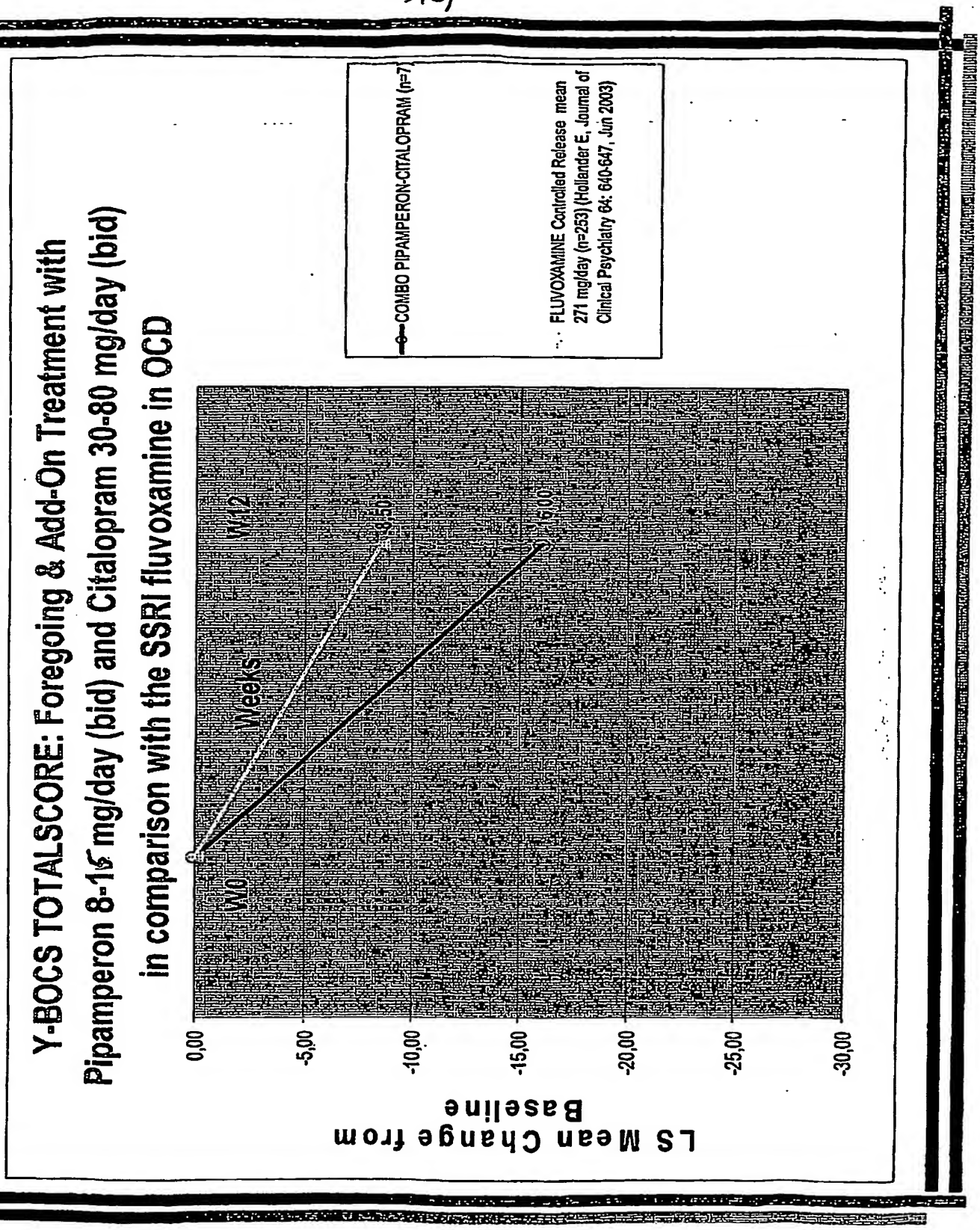
Y-BOCS TOTALSCORE: Foregoing & Add-On Treatment with
Pipamperon 8-15 mg/day (bid) and Citalopram 30-80 mg/day (bid)
in comparison with the SSRI fluvoxamine in OCD
COMBO PIPAMPERON-CITALOPRAM (n=7)
FLUVOXAMINE Controlled Release mean
271 mg/day (n=253) (Hollander E, Journal of
Clinical Psychiatry 64: 640-647, Jun 2003)
LS Mean Change from
Baseline
0,00
-5,00
-10,00
-15,00
-20,00
-25,00
-30,00
W0
W12
Weeks
-9,50
-16,00

Figure 12

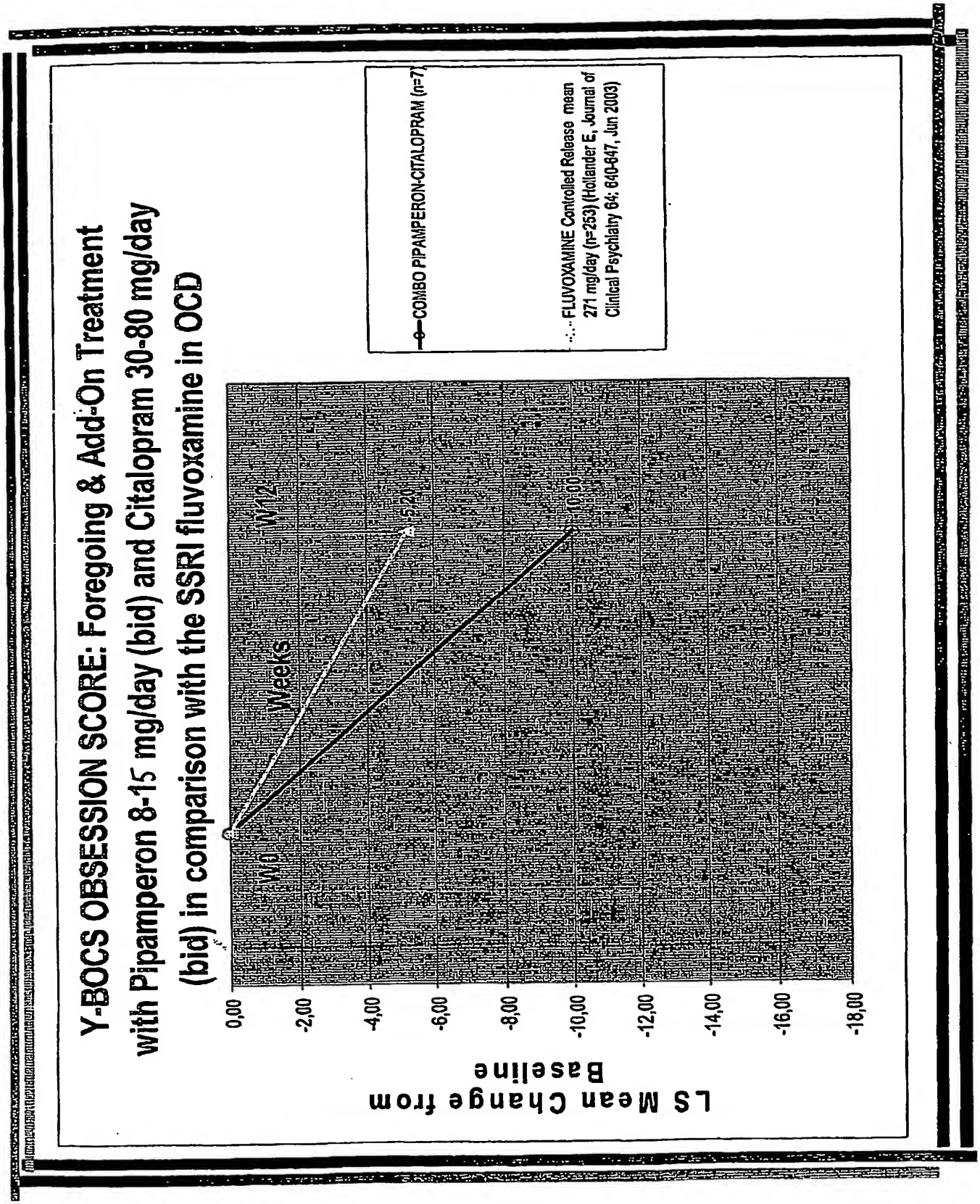
Y-BOCS OBSESSION SCORE: Foregoing & Add-On Treatment with Pipamperon 8-15 mg/day (bid) and Citalopram 30-80 mg/day (bid) in comparison with the SSRI fluvoxamine in OCD
LS Mean Change from Baseline
0,00
-2,00
-4,00
-6,00
-8,00
-10,00
-12,00
-14,00
-16,00
-18,00
W0
W12
Weeks
-5,20
-10,00
COMBO PIPAMPERON-CITALOPRAM (n=7)
FLUVOXAMINE Controlled Release mean 271 mg/day (n=253) (Hollander E, Journal of Clinical Psychiatry 64: 640-647, Jun 2003)

Figure 13

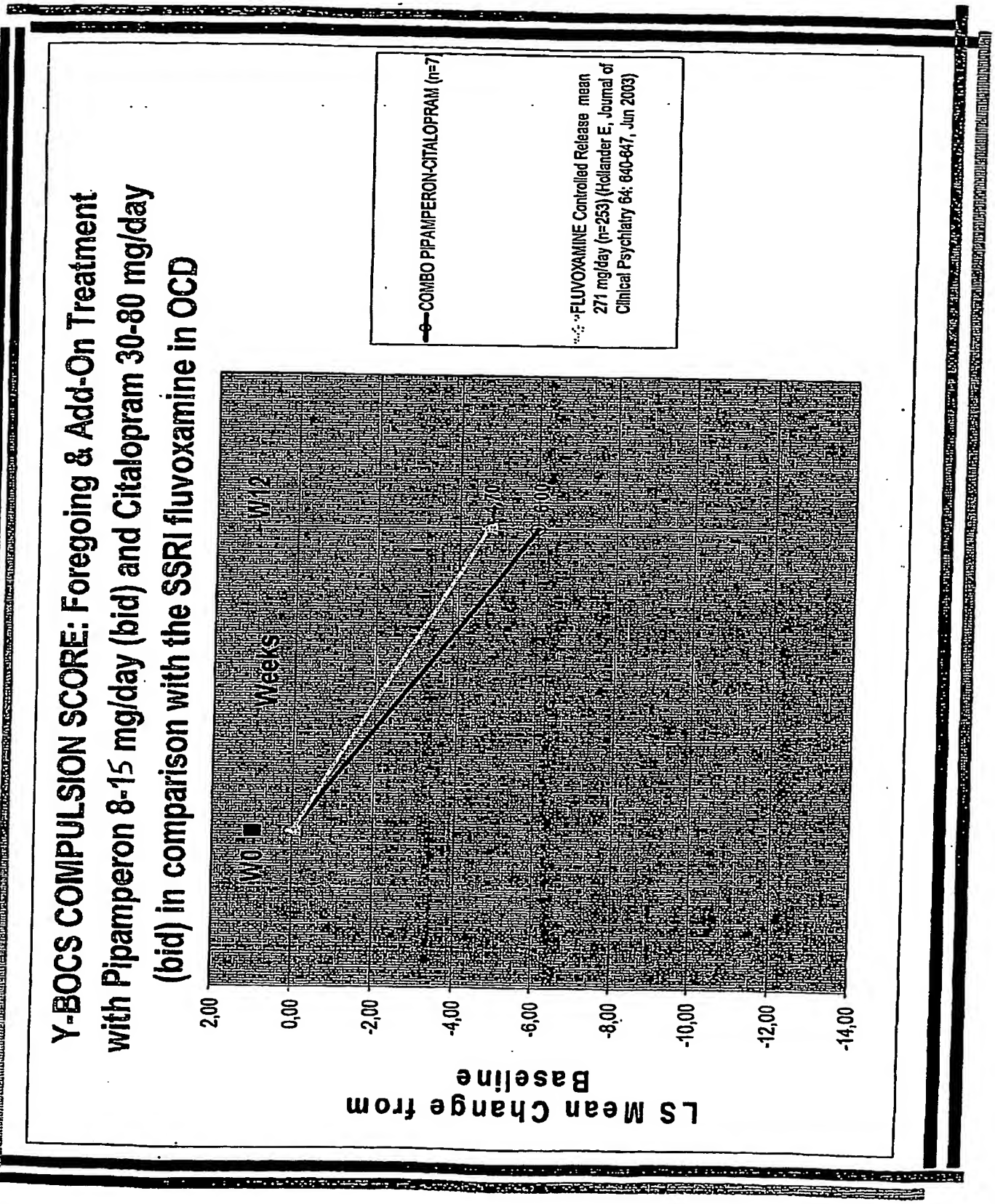
Y-BOCS COMPULSION SCORE: Foregoing & Add-On Treatment with Pipamperon 8-15 mg/day (bid) and Citalopram 30-80 mg/day (bid) in comparison with the SSRI fluvoxamine in OCD
LS Mean Change from Baseline
2,00
0,00
-2,00
-4,00
-6,00
-8,00
-10,00
-12,00
-14,00
Wo
W12
Weeks
COMBO PIPAMPERON-CITALOPRAM (n=7
FLUVOXAMINE Controlled Release mean 271 mg/day (n=253) (Hollander E, Journal of Clinical Psychiatry 64: 840-847, Jun 2003)

Figure 14

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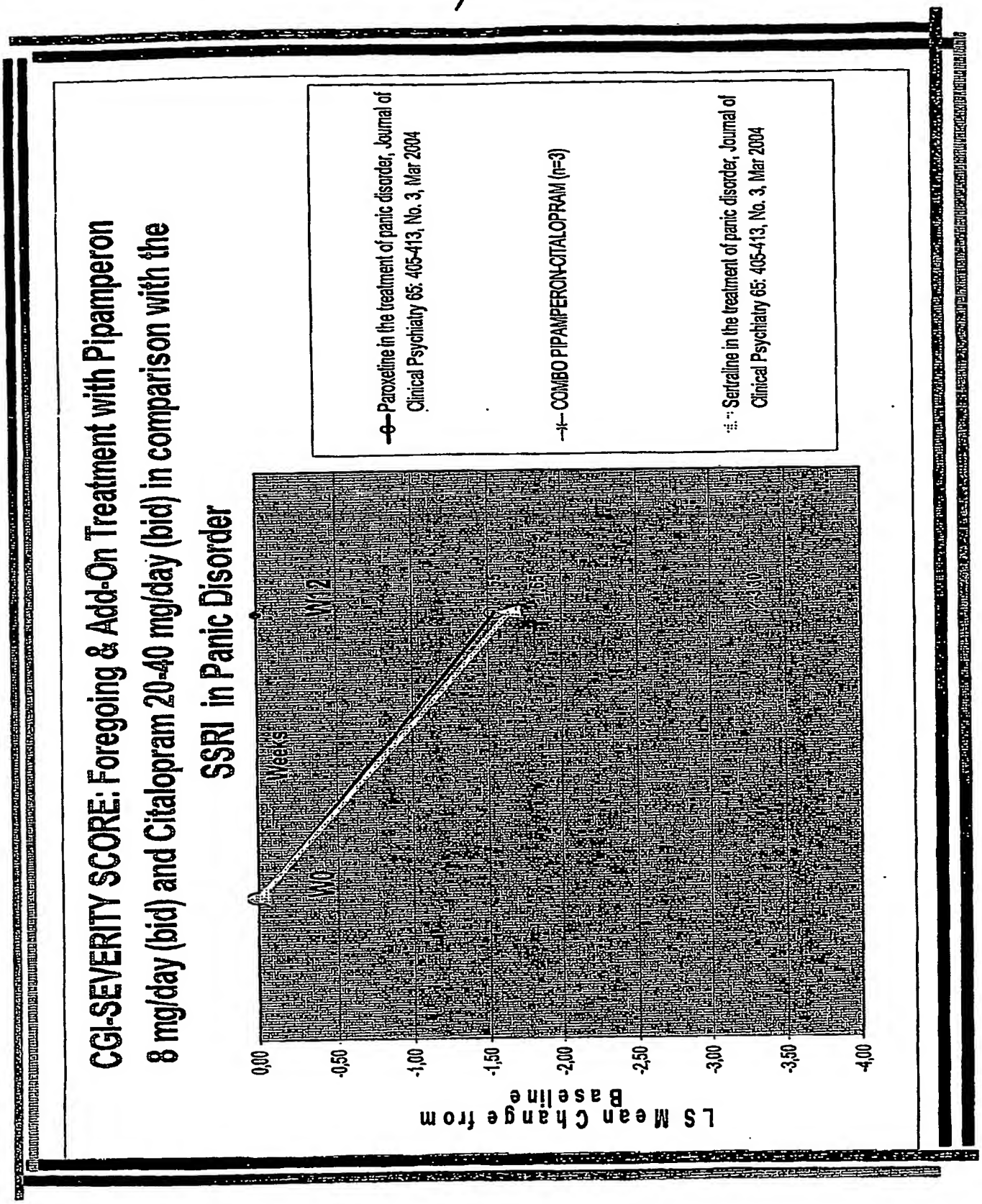

Figure 15

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